B003102

REPORT TITLE

The 30-Day Response by the Endosulfan Task Force to the Environmental Fate and Ecological Effects (EFED) Drafted Risk Assessment for the Reregistration Eligibility Decision On Endosulfan (EFED Memorandum Dated October 30, 2000)

DATA REQUIREMENT

Not Applicable

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REPORT DATE

December 14, 2000

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STATEMENT OF NO DATA CONFIDENTIALITY CLAIMS

No claim of confidentiality is made for any information contained in this study on the basis of its falling within the scope of FIFRA §10(d)(1)(A), (B), or (C).

Report Title: The 30-Day Response by the Endosulfan Task Force to the Environmental Fate and Ecological Effects (EFED) Drafted Assessment for the Reregistration Eligibility Decision On Endosulfan (EFED Memorandum Dated 10/30/00)

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Date:	December 14, 2000

STATEMENT OF GOOD LABORATORY PRACTICE

No Good Laboratory Practice Statement is required for the information presented in this volume according to 40CFR Part 160.

Submitter: _____

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Date: _____

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Report Title: The 30-day Response by the Endosulfan Task Force to Environmental Fate and Ecological Effects (EFED) Drafted Risk Assessment for the Reregistration Eligibility Decision on Endosulfan (EFED Memo Dated October 30, 2000)

I. INTRODUCTION

The Endosulfan Task Force (ETF) companies consisting of Aventis CropScience USA LP, FMC Corporation and Makhteshim-Agan of North America Inc. prepared this 30-day response to EPA's 'Environmental Fate and Ecological Effects Risk Assessment for the Reregistration Eligibility Decision (RED) on Endosulfan' (EFED memo dated October 30, 2000; DP Barcodes - D238673, D191905, D224730, D198346, D259123, D259983, D260709, D262998).

While EPA asks us to address only errors, identify confidential business information, and inform the Agency of any newly completed, pending and planned studies, it is the belief of the Endosulfan Task Force that the current EFED draft assessment (dated 10/30/00) requires us to provide a broad and comprehensive response. Based on careful reviews, we believe that the current draft EFED Chapter contains significant errors and is composed of many statements which will mislead the public. If the current statements and the overall impression created by EFED for endosulfan remain unchanged, it will be difficult to achieve an objective and science-based evaluation for all endosulfan stakeholders. Therefore, we have identified in the response document the errors as well as the several issues that require further discussions with the Agency. We respectfully request EFED to revise the risk assessment contents before releasing the draft RED document to the public docket. Specifically, we request EFED to review and consider our response regarding contents, correct errors, remove misleading statements, and revise the input parameters used for calculating the estimated environmental concentrations (EECs) for endosulfan resulting from the current labeled uses.

II. Task Force Response to the Data Gaps Listing as Identified by EFED

EPA requires a number of studies to be performed by the ETF. Based on existing studies to be submitted to EPA it can be established that endosulfan sulfate is as toxic to fish and aquatic invertebrates as the parent compound(s). Therefore a risk assessment could be based on the toxicity of α-endosulfan and β-endosulfan without the performance of additional studies with the sulfate. ETF is therefore respectfully requesting to modify the study requirements as follows:

Study Requirement	**Requested Modification and Justification**
Avian acute oral tox in bobwhite and mallards with endosulfan sulfate	Studies will be performed
Avian dietary tox in bobwhite and mallards with endosulfan sulfate	Studies will be performed
Avian reproduction in bobwhite and mallards with endosulfan sulfate	The study request should be retracted. As the sulfate is also a metabolite in animals, the toxicity of the sulfate is included in the parent studies. These studies should only be required if acute studies show higher toxicity than the parent compound.
Acute tox in rainbow trout and bluegill with endosulfan sulfate	Studies in rainbow trout and carp indicating similar toxicity as parent are available and will be submitted. A study in bluegill will be performed.

Study Requirement	Requested Modification and Justification
Acute tox in daphnia with endosulfan sulfate	A study in daphnia is available and will be submitted.
Fish full life cycle in rainbow trout with endosulfan sulfate	The study request should be retracted. Available acute data of endosulfan sulfate in fish (to be submitted) indicate similar toxicity of the degradation product as the parent. A FLC study with the parent compound in fathead minnows, the preferred guideline species, is available and has been accepted.
Acute tox in marine/estuarine fish with endosulfan sulfate	The study request should be retracted. The degradation product can be regarded of equal toxicity as parent
Acute tox in mysid shrimp with endosulfan sulfate	The study request should be retracted. The degradation product can be regarded of equal toxicity as parent.
Acute whole sediment tox in freshwater invertebrates with endosulfan	A study will be performed
Acute whole sediment tox in freshwater invertebrates with E-sulfate	A study will be performed
Acute whole sediment tox in marine/estuarine invertebrates with endosulfan	A study will be performed
Acute whole sediment tox in marine/estuarine invertebrates with E-sulfate	A study will be performed
Chronic whole sediment tox in freshwater invertebrates with endosulfan	Study should only be required if acute studies show higher toxicity of the parent compound. The sulfate is the more likely metabolite occurring in the sediment.
Chronic whole sediment tox in freshwater invertebrates with E-sulfate	A study will be performed
Chronic whole sediment tox in marine/estuarine invertebrates with parent	A study should only be required if the acute studies show higher toxicity of the parent compound. The sulfate is the more likely metabolite occurring in the sediment.
Chronic whole sediment tox in marine/estuarine invertebrates with e-sulfate	Study will be performed

III. Task Force Response to the Various Sections of the EFED Risk Assessment for Endosulfan

Detailed below is the full response by the Endosulfan Task to the Environmental Fate and Effects Division Draft Chapter on Endosulfan.

The ETF realizes that risk assessments for endosulfan are particularly challenging given the wide range of crops treated and long history of use of the compound resulting in a large database of literature information and incident reporting. Endosulfan, however, has a key role in insect resistance management and integrated pest management programs. Over the last two decades, the ETF has developed a comprehensive database in support of many of these valued uses. We have been working with the Agency and grower community to alter product use patterns, incorporate mitigation measures and develop stewardship programs so that growers have access to a critical tool that can be used in a safe and effective manner. ETF's detailed comments demonstrate that the "Executive Summary" does not reflect current use patterns. It is selective and at times scientifically incorrect in conducting the preliminary environmental exposure and ecological effect assessments.

ETF is therefore asking the Agency to review our specific comments and rewrite the Executive Summary to reflect present day usage, use sound scientific principles rather than opinion, remove inappropriate comparisons and to be internally consistent with the Health Effects Division Chapter. To publish this Executive Summary as it stands, will mislead the public who does not have full knowledge of the database. It is important that all decisions for the endosulfan reregistration process be made using "best available science" rather than by subjectivity.

Our key comments concerning the Executive Summary which are detailed in our full response are:

- The assessment was not "non-conservative" based on current day usage.
- The chemical's persistence was considerably over-estimated.
- Monitoring studies do not confirm a widespread contamination of surface water or ground water from current US labeled uses.
- Incident reporting does not reflect the widespread improvement in recent years with revised use directions and improved stewardship.
- The current runoff buffer was not included in the assessment
- The comparison with five other chemicals considered to be alternatives was inappropriate and contrary to the Science Advisory Panels advice.
- The assumptions made for aquatic work are very conservative.
- Endosulfan is constantly implied to be an endocrine disrupter or considered a reproductive and developmental toxin, which is clearly the opposite of HED's conclusions:

  - " *... conclusions by EPA as to whether endosulfan is an endocrine disrupter cannot be made at this time*"…

- "*The data base is complete and there are no data gaps pertaining to developmental or reproductive toxicity. The data provided no indication of increased sensitivity of rats or rabbits to in utero and post-natal exposure to endosulfan.*"

We trust that EPA will take full note of our specific comments and ensure that the Executive Summary is up-to-date and science based.

EPA EFED memorandum

Page 3

EPA comment: *"Endosulfan and its degradate, endosulfan sulfate, are known to leach through soil into ground water under certain conditions as a result of label use. Use of this chemical in areas where soils are permeable, particularly where the water table is shallow, may result in ground-water contamination."*

ETF response: The ETF does not believe that that this proposed Groundwater Advisory is appropriate. Endosulfan has not exhibited mobility in field studies that warrants such an advisory and it is strongly adsorbed to soil particles. The detection reported in the Pesticides in Ground Water database are considered to be spurious and may have occurred due to spray equipment filling/cleaning near an improperly capped/sealed well or may be due to preferential flow into shallow aquifers or other rare situations that are not particular to the environmental fate properties of endosulfan.

EPA comment: *"**Surface Water Label Advisories.** This product may contaminate water through drift of spray in wind. This product has a potential for runoff according to the pesticides "mean" soil partition coefficient (K_d) for several months or more after application. Poorly draining soils and soils with shallow watertables are more prone to produce runoff that contains this product."*

ETF response: The ETF does not believe that it is appropriate to define the surface water label advisory at this time whilst many of the conclusions made by EFED have been challenged by the ETF. The ETF believes that appropriate language already exists on end-use product labels, which include the need for a 300-foot buffer. Modifications to advisories should be drafted at the conclusion of the risk assessment and management process.

Executive Summary

Page 5

EPA comment: *"Based on a non-conservative screening level assessment…"*

ETF response: This statement is incorrect and should be changed. The endosulfan exposure assessment conducted by the EPA using PRZM/EXAMS modeling does not reflect realistic use conditions and scenarios (details are presented below in the specific sections). The risk quotients resulted from unrealistic exposure estimation. They have no relevance to realistic worst case conditions. Two of the chosen scenarios (lettuce in Tennessee and grapes in New York) are not representative of the use of endosulfan in these crops. The

ETF has presented a systematic modeling effort that included scenario selection, model input parameters sensitivity analysis and calibration and validation of buffer simulation that yielded exposure estimates that we consider to be realistic worst case scenarios. The risk quotients calculated by EPA resulted from unrealistic exposure estimation. They have no relevance to realistic worst case conditions as no attempt has been made to account for the effect of the label requirement for a 300 foot buffer on runoff.

EPA comment: *"Based on a non-conservative screening level assessment…"*

ETF response: This statement is incorrect and should be changed. EFEDs endosulfan exposure assessment using PRZM/EXAMS modeling does not reflect realistic use conditions and scenarios (details are presented below in the specific sections). Two of the chosen scenarios (lettuce and grapes) do not represent major crop/use regions. ETF has presented a systematic modeling effort that included scenario selection, model input parameters sensitivity analysis and calibration and validation of buffer simulation that yielded exposure estimates that are realistic worst case scenarios. The risk quotients resulted from unrealistic exposure estimation. They have no relevance to realistic worst case conditions.

EPA comment: "*The chemical's persistence coupled with its documented atmospheric transport has rendered sites both adjacent to and remote from use areas vulnerable to the effects of this very highly toxic pesticide."*

ETF response: Based on the results of field monitoring program results, endosulfan cannot be classified as persistent. Based on a number of publications not used by EPA, endosulfan is detectable only in very low concentrations in the air during the time of application and decreases to extremely low levels during off-season. The extremely low traces occasionally found in remote areas were not confirmed in each reported case.

EPA comment: *"Monitoring studies confirm widespread contamination of surface water."*

ETF response: The surface water monitoring results after the introduction and implementation of use restrictions (between 1988 and 1993) show significantly lower concentrations of endosulfan residues in surface water that are well below the contamination level (MCL). A detailed analysis is presented in Appendix 1.

EPA comment: *"Incident data also confirm EFED's expectation that endosulfan's current use represents a serious risk of non target mortality for aquatic species."*

ETF response: This statement is not justified. After the change in application rates (maximum of 3 lbs a.i./Acre per year) and incorporated label mitigation measures (especially in California), the incident database does not confirm EPA's concern regarding risk through endosulfan registered uses.

EPA comment: *"EFED conducted a more refined risk assessment using probabilistic risk assessment techniques based on actual reported application rates in California coupled with a 300-ft spray drift buffer."*

ETF response: The buffers were established as exposure mitigation requirements in the labels not only for reducing spray drift, but also runoff. The effect of the 300-ft buffer on runoff

reductions was not considered in EPA's refined risk assessment leading to a skewed conclusion. Several studies found in the literature and the studies submitted by ETF indicate significant reduction of exposure concentrations through runoff and spray drift caused by the effectiveness of a buffer strip.

EPA comment: *(probability estimates)*

ETF response: These numbers should be changed after a refinement of exposure concentrations in consideration of realistic conditions as outlined by the ETF assessment submitted to EPA.

EPA comment: *"Additionally, a comparative risk assessment of endosulfan and 5 other chemicals considered to be alternatives (esfenvalerate, imidocloprid, dimethoate, methomyl and spinosad), endosulfan rated as the most likely to pose the greatest overall risk to birds and aquatic organisms."*

ETF response: The comparative risk assessment should be deleted. The selection of competitor products seems arbitrary. Data input and assumptions are not transparent. The assessment performed does not take into account the full label restrictions on endosulfan. Neither the full pest spectrum of the competitors nor the benefits of endosulfan in Integrated Pest Management programs were considered.

EPA comment: *"…the assumptions for this assessment are not particularly conservative."*

ETF response: This statement is incorrect and should be changed. As pointed out above, the endosulfan exposure assessment conducted by the EPA using PRZM/EXAMS modeling does not reflect realistic use conditions and scenarios.

EPA comment: *"… endosulfan's capacity to act as an endocrine disruptor …"*

ETF response: This part of the sentence should be deleted. Only in-vitro studies indicate a low affinity of endosulfan to the endocrine receptors. In-vivo studies including a vitellogenin study in fish indicate that there is no endocrine disruption by endosulfan. A detailed response can be found below in the ETF response to Appendix K.

EPA comment: *"The sensitivity of the surrogate species may not however, be representative of the most vulnerable organisms."*

ETF response: The reference to the sensitivity of the surrogate species should be deleted. The use of "surrogate species" is standard practice in all ecotoxicological testing and risk assessment.

EPA comment: *(Last paragraph)*

ETF response: If EPA would use truly non-conservative assumptions (e.g. considering the 300 ft runoff buffer, field half-lives etc.) the conclusions presented in the paragraph would NOT result in unacceptable risks.

EPA comment: *"Due to the chemical's persistence and documented atmospheric transport, endosulfan may pose risks to sites remote from usage areas."*

ETF response: The concentrations measured in remote areas are very low and are well below any ecological effects threshold concentrations and thus do not pose a risk to remote from usage areas.

EPA comment: "… *chronic RQ values ranging as high as 697…"*

ETF response: The highest RQ values is "487", as stated on page 23, not "697". Also this value is based upon exposure assessments which the ETF contests do not even represent the realistic worst-case.

EPA comment: *"… current endosulfan use rates on 88% of the crops modeled will exceed acute high risk LOCs more than 99% of the time. "*
"…chronic RQ values ranging as high as 697 also make it likely that endosulfan will result in possibly chronic effects."

ETF response: This statement is not justified. If the assumptions of such high risks would be true, many more incidents should be reported from actually registered uses of endosulfan.

EPA comment: *Given the reproductive and developmental effects of endosulfan coupled with the chemical's ability to bind to the human estrogen receptor, these chronic effects could have a considerable impact on non target organisms, including humans*

ETF response: This statement is misleading and should be deleted. In the HED Risk Assessment for Endosulfan RED document (Barcode D250471, 2/17/00), it was stated that HED has thoroughly evaluated data on the developmental and reproductive toxicity of endosulfan in mammals. HED determined that endosulfan was not a developmental or reproductive toxicant, and concluded: "*The data base is complete and there are no data gaps pertaining to developmental or reproductive toxicity. The data provided no indication of increased sensitivity of rats or rabbits to <u>in utero</u> and post-natal exposure to endosulfan.*" Based on the complete database, HED stated again, in the Executive Summary, that "*Results from development and reproductive toxicity studies conducted under OPPTS guidelines do not show increased or special sensitivity of the fetus or offspring to the toxicity of endosulfan*"

While endosulfan has been shown to have very weak estrogen binding potential in *in vitro* screening assays, scientific groups such as the Endocrine Disrupting Screening and Testing Advisory Committee (EDSTAC) and the OECD Task Force for Endocrine Disrupter Testing and Assessment (EDTA) have emphasized that this type of screening data has limited predictive capabilities. Therefore, before a definitive finding of endocrine disruption can be made, evaluation through in vivo screening and testing must be conducted and a weight-of-evidence determination concluded from all available data. In addition, the data cited used assays that have been determined to be too unreliable for regulatory screening purposes, and the results have not been supported by data generated from a multitude of valid *in vivo* screening and testing methods. As stated by HED, until EPA has completed the development of criteria for the evaluation of endocrine disruption, the classification of a chemical as an endocrine disrupter is scientifically

inappropriate. The ETF strongly believes that a full evaluation of available data for endosulfan will clearly show that endosulfan is not an endocrine disrupter.

Introduction

Page 1

EPA comment: *"Endosulfan is a chlorinated hydrocarbon insecticide…"*

ETF response: EPA classifies endosulfan as a "chlorinated hydrocarbon". Endosulfan has been classified as a "*sulphite* or as *dioxathiepin*" by IUPAC and in the Chemical Abstracts. Further, the World Health Organization (WHO) has confirmed this by classifying endosulfan as the *sulfurous acid ester of a chlorinated cyclic diol*. The Task Force respectfully requests that the classification be changed as the term "chlorinated hydrocarbon" is generally used to characterize chemicals with specific properties (e.g. POPs), which endosulfan does not share.

Page 1

EPA comment: *"Endosulfan is formulated into emulsifiable concentrate, wettable powder, ultra-low volume (ULV) liquid spray, and smoke tablets."*

ETF response: The Endosulfan Task Force (ETF) is not supporting the above-mentioned ULV liquid spray, the insecticidal smoke tablets or similar impregnated materials containing endosulfan. The ETF members submitted requests in 1999 and amend the ETF technical labels to delete these and other non-food, non-agricultural uses. The official Notice for the use-deletions was published in Federal Register on July 19, 2000. The 30-day commenting period has since expired and the use deletions should become effective after January 2001.

Page 1

EPA comment: *"…endosulfan may be found in formulations with dimethoate, malathion, methomyl, monocrotophos, pirimibcarb, triazophos, fenoprop, parathion, petroleum oils, and oxine-copper."*

ETF response: The ETF does not support any of those listed combination products.

Environmental Fate Assessment

Page 2

EPA comment: "*endosulfan represents a mixture of two chemically distinct pesticides…*"

ETF response: This is a misleading term and should be rephrased. This implies that technical grade endosulfan has two different compounds, where as in fact it contains one compound, exhibiting isomerism. The sentence could be rephrased as ". . . technical grade endosulfan represents a mixture of two biologically active isomers that differ in physico-chemical properties."

Page 2,

EPA comment: *"The estimated half-lives for the combined toxic residues (endosulfan plus endosulfan sulfate) ranged from roughly 9 months to 6 years."*

ETF response: This statement is a misrepresentation of facts. Due to the limited size of the soil samples in the standard laboratory studies, the microbial activity decreases within 3 – 4 months. As a consequence, laboratory half-lives in long-term studies are frequently overestimated. Therefore, half-lives from field studies are more realistic. The combined endosulfan isomers and endosulfan-sulfate were found to degrade with overall half-lives ranging from 26 to 176 days based on the terrestrial dissipation studies submitted by the ETF (Hacker (1989,MRID# 41309702), Mester (1990, MRID# 41468601), and Czarnecki & Mayasich (1992, MRID# 43069701)).

Page 2

EPA comment: "*Within the water bodies, endosulfan tends to be sorbed onto sediment and plants. The sorbed endosulfan may be slowly released back into the water*."

ETF response: This statement should be deleted. Barry and Logan (1998) speculated: "*Dying plant species may have also been an important source for the slow release of endosulfan back into the microcosms*", but did not offer any proof. The release of absorbed endosulfan from dying macrophytes was not investigated in this study. The concentration of endosulfan measured in the microcosms follows a smooth decline pattern and did not suggest slow release into water phase from any adsorbed source. The study notes that only 6 to 12 % of the applied endosulfan (as endosulfan and endosulfan sulfate) was present in the macrophytes at the end of the study. The study also notes that metabolism of endosulfan in the macrophytes and algae as significant route of degradation. Therefore, if there is a potential for endosulfan to be released back into water upon dying of macrophytes, the amount that will be available for release will be what is left from degradation in the macrophyte tissue and will be infinitesimal.

Page 3

EPA comment: "*Table 1"*

ETF response: The results of a number of studies submitted by the ETF should also be listed:

water solubility - MRID# 41421502
vapor pressure -MRID# 41421501
octanol/water coefficient - MRID# 41421503
photolysis in water - MRID# 41415700
aerobic aquatic metabolism – MRID# 44917802
batch equilibrium – MRID# 41412905
runoff studies - MRID# 41309701, 44903601
farm pond study - MRID# 41164101

Page 4,

EPA comment: ***Table 1*** *Parameter "Accumulation in Fish",*
"2429X for edible tissue and 2755X for whole body of mullet (Mugil cephalus)"

ETF response: Delete "fish" in the column "Parameter", in as mussel are mentioned under "Value" The accumulation factor for edible tissue should be 2249 instead of 2429. It also should be added that there was no detection of residues after 48 h of depuration.

Page 4

EPA comment: *"The estimated half-lives for the combined toxic residues (endosulfan plus endosulfan sulfate) ranged from approximately 300 days to greater than 2000 days."*

ETF response: The appropriate references are missing (MRID# 43812801). It should also be added that the half-life for endosulfan sulfate of 300 to 2000 days was obtained under confined laboratory conditions (c.f. ETF response to the corresponding EPA comment on page 2).

Page 5

EPA comment: "*The persistence of endosulfan appears to increase under anaerobic conditions."*

ETF response: The reference is missing (MRID# 41412904).

Page 5

EPA comment: "*In an aerobic aquatic metabolism…"*

ETF response: The reference is missing (MRID# 44917801).

Page 5

EPA comment: "*Batch Equilibrium studies suggest….*

ETF response: The reference is missing (Goerlitz, 1988, MRID# 41412905, 41412906).

Page 6

EPA comment: *"Published literature (see Appendix B)…*

ETF response: Additional important publications need to be considered for this chapter (Bidleman et al.,1990, Organic Contaminants in the Northwest Atlantic Atmosphere at Sable Island,1988-1989, Chemosphere; 1992, p.1389-1412; Hoff et al., 1992; Annual Cycle of Polychlorinated Biphenyls and Organohalogen Pesticides in Air in S. Ontario; Environm.Sci.Technology; 1992, 26,2; 166-175; Simonich & Hites, 1995; Global Distribution of Persistent Organochlorine Compounds; Science; 1995; 269; 1851-1854). Based on these publications Endosulfan is detectable only in very low concentrations in the air during the time of application and decreases to extremely low levels during off-season. The extremely low traces occasionally found in remote areas were not confirmed in each case.

Page 7,

EPA comment: *Table 2*

ETF response: Half-lives for total Isomers (α+ β) are different in the reports compared to what is presented in Table 2. Values should be changed accordingly.

Trial	EFED value	Report value
Donaldsville (bare ground)	172	76
Donaldsville (tomatoes)	155	75
Tulare county (bare ground)	89	97
Tulare county (cotton)	93	90
Poplar (bare ground)	nd	9-13
Poplar (cotton)	nd	10-15

Page 7

EPA comment: "*Despite these limitations, dissipation of endosulfan in the field studies was within the same magnitude as would be predicted from laboratory soil metabolism studies"*

ETF response: This statement is only true with regard to the parent isomers. The degradation of the sulfate in the field is significantly faster than measured in the laboratory with the limited microbial activities in long-term studies. As a consequence, field half-lives should be used in the modeling in order to consider the exposure of the combined endosulfan residue of relevance (α, β and endosulfan-sulfate).

Page 7

EPA comment: (*Runoff*)

ETF response: Please add the runoff study performed in Kentucky,1999 (MRID# 44903601). An additional runoff study was conducted in South Carolina in 1989 (MRID# 41309701) with a 200 foot vegetative buffer strip. This study demonstrated that a vegetative buffer (200 ft) can reduced the Endosulfan concentration in the runoff by two orders of magnitude!

Page 8

EPA comment: ***Foliar Dissipation***

ETF response: MRID# 44403102 should be added to the citations and used for modeling. The results from this study indicate foliar half-lives of 0.6 – 3 days.

Page 8

EPA comment: ***Aquatic Dissipation***

ETF response: In addition to the cited microcosm study the ETF also conducted a farm pond study in 1989 (MRID# 41164101; Cornaby, 1989), which was accepted by EPA fulfilling the Reference Guideline # 72-7b. This study was conducted under "worst case" conditions (did not reflect 300 ft buffer). We believe that the subject study is important for the EFED risk assessment. Very high concentrations of Endosulfan in the runoff water (>220

ppb) were diluted by a factor of 100 (peak concentration in the pond was 1.3 ppb). Only higher concentrations caused some fish kill in the shallow areas where the runoff entered the pond. By adding a "300 foot buffer" as presently on the label, these effects would likely have been totally mitigated.

Page 8,

EPA comment: "*Major routes of dissipation noted in the study were sorption to sediment, degradation by bacteria, and reversible uptake/sorption by macrophytes and algae"*

ETF response: In this place, no reference is provided for the reversibility of this process. This statement is presumably based on Barry and Logan (1998). It should be noted that release of absorbed endosulfan from dying macrophytes was not investigated in this study. A statement *"Dying plant species may have also been an important source for the slow release of endosulfan back into the microcosms*" stated in the paper is a speculative comment (see above for a more detailed ETF comment on this issue). Because of the speculative nature of the statement, the second half of the sentence should be deleted.

Page 8

EPA comment: *"… on striped mullet, the bioconcentration factors were ~2400X for combined isomers in edible tissues*"

ETF response: A reference should be added. The bioconcentration factor was 2200X, not 2400X. There should also be mention of the fact that the residues in fish are completely depurated after 48 h in clean water.

Page 8/9

EPA comment: *Quality of data* (The paragraphs are numbered arbitrarily)

ETF response: The numbering of paragraphs should be deleted.

Water Resource Assessment

Page 9

EPA comment: "*With repeated applications, or even applications in consecutive years, endosulfan may accumulate in the soil,*"

ETF response: From monitoring studies (Tiirmaa & Dorn, 1988) covering different geographical areas and conditions it can be concluded that endosulfan does not accumulate in soil or form a concentration plateau of ecotoxicological relevance in soils even after extensive and consecutive use for several years under normal agricultural practices. The report will be submitted by the ETF.

Page 9

EPA comment: *"Published literature suggests that endosulfan may also be sorbed/taken up by macrophytes and algae and released back into the water column when these plants die*"

ETF response: As argued above (ETF response "page 2" to this issue), this sentence should be deleted due to the speculative nature of the statement cited.

Page 9

EPA comment: *"Existing water monitoring data confirm the presence of endosulfan residues in surface and ground water on a qualitative basis. Because endosulfan is persistent in neutral to acidic soils for months, the pesticide will be susceptible to transport via runoff for prolonged periods after initial application."*

ETF response: The latter part of this statement is not correct, when it comes to quantitative assessments. As already stated earlier in HED's drafted risk assessments (under Monitoring Data: 4.3.b.2; page 35) it was stated: "*The monitoring data indicate, however, that EFED's simulation models tend to overestimate actual concentrations of Endosulfan residues in surface and groundwater".* Based on all available monitoring data for Endosulfan from various water treatment plants, most of the detects were between 0.009 and 0.6 ppb.

Page 9

EPA comment: *"With repeated applications, or even applications in consecutive years, endosulfan may accumulate in the soil"*

ETF response: Long-term field accumulation studies in different regions of the world (Tiirmaa & Dorn, 1988) have shown that endosulfan after yearly application of 5.5 to 12.5 kg/ha over a period of 5 to 7 years dissipates within 6 months after the last application to a total residue level of less than 0.1 ppm (soil 0-10 cm). There is no soil accumulation of endosulfan, even after excessively high application rates over many years.

Page 9

EPA comment: *"Because of its tendency to sorb onto soil, endosulfan should not be frequently detected in ground water; however, endosulfan is a persistent chemical, and available monitoring data has revealed endosulfan detections in well"*

ETF response: This statement is misleading, of very qualitative nature, and should be rephrased. If one evaluates the total numbers in the available surveys (USEPA, 1992), the number of positive detections are insignificant (1.3%), as well as the concentrations range from <0.005 to 20 ppb. Again referring to HED's recent risk assessment (under Monitoring Data: 4.3.b.2; page 35), it was stated that *"an analysis of the EPA STORET database conducted in 1985 showed that of 850 well water samples analyzed, none contained detectable residues of endosulfan sulfate".* The ETF will provide a further response to this comment during the 60-day comment period.

Page 10

EPA comment: *"The pesticide was not included in the U.S. Geological Survey National Water Quality Assessment (NAWQA) program"*

ETF response: Endosulfan was included in NAQWA program since the time of its initiation (1991). However, the monitoring results were not reported in the prior NAWQA reports. See Appendix 1 for an analysis of the monitored endosulfan data from the NAWQA database.

Page 10

EPA comment: *"contaminated numerous surface- and ground water bodies throughout the US"*

ETF response: There is no scientific basis for this statement and should be removed. The ground water detection reports (Pesticides in Ground Water (1997-91) should be viewed on a qualitative basis. It should also be noted that only in about 0.1 to 1.3 % of the sampled wells endosulfan residues were detected, and all of the detections were well below the level of contamination (MCL). Also, most of the detections reported are at concentrations below the Limits of Quantification (LOQ). Endosulfan does not have intrinsic potential to leach due to its high partition coefficient (Koc > 10,000) and low solubility (≤ 0.33 mg/L). The detection reported in the Pesticides in Ground Water database may have occurred due to spray equipment filling/cleaning near an improperly capped/sealed well or may be due to preferential flow into shallow aquifers or other rare situations that are not particular to endosulfan.
The surface water monitoring results after the introduction and implementation of use restrictions (between 1988 and 1993) show significantly lower concentrations of endosulfan residues in surface water and are also well below the contamination level (MCL) – See Appendix 1.

Page 10

EPA comment: *(Use of STORET database)*

ETF response: EFED had analyzed all the available monitoring data in STORET in a lumped manner. However, it should be analyzed in chronological manner. This will highlight the effect of the introduction of the label restrictions on the levels of endosulfan detected in the surface waters. See Appendix 1 for a chronological analysis of STORET monitoring data, which shows that the introduction of use restrictions resulted in significantly lower concentrations and in most cases that no endosulfan residues were detected in surface waters.

Page 12

EPA comment: *"technical use labels for endosulfan include language for a 300-foot spray drift buffer to minimize spray drift" "While OPP has calculated EECs based on the assumption of no spray drift, it notes that this practice is not reflected in many of the end-use labels."*

ETF response: This statement is wrong. The use labels for all ETF products include the language for a 300-foot buffer to minimize runoff and spray drift. It does not limit exposure to only drift but effectively mitigates also runoff.

Page 12,

EPA comment: *Table 3*

ETF response: The label rate for lettuce is 3 x 1.0 lb. a.i/A instead of 2 x 1.5

Page 12, footnote 4 to table 3

EPA comment: *"[4] Simulations in these states do not represent a major crop/use area for endosulfan, but likely represent more conservative estimates of EECs.*

ETF response: As noted by EPA, these scenarios do not represent major crop/use areas. This is just not a conservative assumption, but will produce unrealistic exposure estimates. It should also be noted that endosulfan use in grapes represents a small portion of the total use. Therefore, the grapes exposure scenario should not be considered and the lettuce scenario should be revised using a more appropriate use area.

Page 13,

EPA comment: *Table 4, Aerobic aquatic metabolism rate*

ETF response: EPA assumed the aerobic aquatic half-life to be 2 times longer than the aerobic soil half-life. This is not correct particularly for endosulfan, which is readily hydrolyzed in water. The aerobic aquatic studies submitted by the ETF (MRID# 44917801 and 44917802) were deemed supplementary studies by the EPA. Therefore, the degradation rate (T½ for α- and β-endosulfan = 12 to 15 days and for total α-, β- and endosulfan-sulfate = 18 to 21 days) in the total sediment/water system from the above study should be used in the PRZM/EXAMS modeling.

Page 13, footnote to table 4

EPA comment: *PRBEN represents the fraction solute sorbed to runoff sediment that does not quickly equilibrate with the water column when the sediment enters the pond. The 0.5 value is an EFED standard for this parameter, and according to recent literature on sequestration of organics to sediments, this is a reasonable value*

ETF response: ETF still believes that a PRBEN value of 0.5 for a compound like Endosulfan (having a high Koc) is inappropriate. If there is any relevant recent literature available as stated by EPA addressing this, it should be quoted in the document. We contest that a value of 0.9 is more appropriate based upon results of microcosm studies with similarly lipophilic compounds. EECs calculated by PRZM/EXAMS are extremely sensitive to changes in this parameter

Page 13

EPA comment: *(Calculation of Endosulfan Sulfate EEC)*

ETF response: The method adopted by EPA to calculate endosulfan sulfate EECs based on the ratio of endosulfan sulfate to α- and β- endosulfan in monitoring data is not appropriate. Endosulfan sulfate is a metabolite of α- and β-endosulfan and is formed as a result of the degradation. EPA's methodology of estimating endosulfan sulfate EECs would violate the mass balance of the endosulfan residues in the system in certain situations. This will particularly be true in the case of peak EECs. Therefore, ETF respectfully requests EPA

to consider the exposure assessments (MRID# 44953102, 44953103, 44953104) for risk assessment.

Page 13

EPA comment: " *buffer is not specifically designed to be a runoff deterrent"*

ETF response: This statement is not true and should be deleted. The buffer zone outlined on the label was also established to minimize runoff. A buffer width of 300 feet (≈ 100 m) is very substantial. This mitigation measure was incorporated into the ETF end-use labels to minimize spray-drift and runoff and was mutually agreed to by the EPA at the time of introduction. Several studies found in the literature show that a vegetative buffer of this magnitude will substantially reduce transport of agricultural chemicals to the water body. The studies conducted by the registrants (MRID# 41309701 and 44903601) show a reduction of up to two orders of magnitude in endosulfan loads as a result of a 200-ft buffer.

Page 13

EPA comment: *"…effectiveness as a runoff reduction cannot be quantified…"*

ETF response: It is a well-established fact that the vegetative buffers reduce sediment loading to water bodies and literature supports this. Recent researches reveal that buffers also mitigate transport of agricultural chemicals through runoff. Studies submitted by the ETF (MRID# 41309701) further confirm these results. The exposure assessment submitted by the ETF in October 1999 (MRID# 44903601) used PRZM to simulate endosulfan loading reduction to the water body. The modeling work was calibrated and validated using the field data from MRID# 41309701 and demonstrated a reduction of 60 – 90% of total endosulfan loading through runoff by the buffer. This proofs that the effectiveness of vegetative buffers on runoff reduction **can be quantified**. ETF respectfully requests the EPA to consider the submitted exposure assessments.

Page 14

EPA comment: *"Table 5"*

ETF response: The EECs should be recalculated. EFED calculated these without considering the effectiveness of the 300-ft runoff buffer and the available field dissipation rates. A number of sensitive parameters chosen by EFED in their exposure assessment are unrealistic and inappropriate:

- In the cotton scenario the curve numbers used were inappropriate. A curve number of 99 would yield higher runoff than from a farm road (PRZM manual Curve Number Table).

- Instead of a PRBEN value of 0.5 for a compound like endosulfan (having a high Koc), a value of 0.9 is more appropriate. If there is any relevant recent literature available as stated by the EPA addressing this issue, it should be quoted in the document.

- Aerobic Aquatic Metabolism Half-Life: EPA assumed the aerobic aquatic half-life to be 2 times longer than the aerobic soil half-life (114 days for α-endosulfan, and 416

days for β-endosulfan). This is not correct, particularly for endosulfan, which is readily hydrolyzed in water. The aerobic aquatic studies submitted by the ETF (MRID# 44917801 and 44917802) were deemed as supplementary studies by the EPA. Therefore, the degradation rate (T½ for α- and β-endosulfan = 12 to 15 days and for total α-, β- and endosulfan-sulfate = 18 to 21 days) in the total sediment/water system from the above study should be used in the PRZM/EXAMS modeling.

Page 14

EPA comment: *"Drinking Water Exposure Assessment"*

ETF response: This chapter should be deleted. The drinking water assessment is already covered in the HED document and of little relevance for assessing the risk to the environment.

Terrestrial Exposure Assessment

Page 16

EPA comment: *Table 8*

ETF response: Instead of theoretical calculations based on Hoerger & Kenaga modified by Fletcher, actual plant residue values should be used. The ETF submitted in 1987 (MRID# 40261301) a risk evaluation of endosulfan to avian species including product specific plant residue data and its crop specific half-lives (123 trials from 18 different crops). This response was submitted in support of the revised maximum label rate (3 lbs./A/year). Assuming a NOEL of 30 ppm (Mallard Duck Reproduction) and given the crop specific half-lives (2.2 to 4.5 days) for total endosulfan measured at day of application (93 ppm) and two weeks thereafter (0.5 ppm) the risk to terrestrial organism is acceptable.

Ecological Effects Assessment

Page 17

EPA comment: *Table 9*

ETF Response: The LD_{50} for bobwhite was reported in MRID# 137189 as 42 mg/kg (as stated on page 86). For ducks, the range of LD_{50} values (28 to 33 mg/kg) for the different studies (see p.86) should be reported instead of just the lowest value.

Page 17,

EPA comment: *Table 9*

ETF Response: A reference for the acute value in rats is missing.

Page 17

EPA comment: *Table 10*

ETF Response: In summary table either means, medians, or ranges should be reported instead of the lowest value; e.g. the available results for the 96hr LC50 Trout using endosulfan technical, range from 0.8 to 1.5 ppb; reported was the lowest value (0.8 ppb). The referenced value for the bluegill sunfish (LC50=1.7 ppb, MRID# 38806) is from a test using pure endosulfan technical (100%). The more appropriate LC50 from testing with 96% technical material should be based on two studies from Pickering & Henderson (MRID# 05014941) with values of 3.3 to 4.4 ppb.
The listed value for the scud is a 96-h value, and not 48-h.

Page 17

EPA comment: *Table 10*

ETF Response: The reference of Mayer & Ellersieck (1986, MRID# 05008271) is not in any reference list.

Page 17

EPA comment: *Table 10*

ETF Response: The values for the Striped Bass (0.1 ppb acute and 0.01 ppb chronic) should be deleted, as it results from a study that is rated "INVALID; temperature fluctuations too great" in the reference list on page 108. The more appropriate study to cite here is the Striped Mullet (LC50= 0.38 ppb; see p.93; MRID# 40228401). This study is classified as core.

Page 18

EPA comment: *"Acute aquatic toxicity estimates ranged from 0.1 to 166 µg/L for endosulfan"*

ETF Response: As a consequence of replacing the values for the Striped Bass with those from the Striped Mullet, the sentence should read now: "Acute aquatic toxicity estimates ranged from 0.38 to 166 ppb for endosulfan"

Ecological Hazard Assessment

Page 18 ff

EPA comment:

ETF Response: Terrestrial and aquatic RQs should be changed. The Agency needs to consider the submitted risk assessment and product specific residue data (see above MRID# 40261301) for these evaluation. We believe that the deterministic approach of calculating single RQs using single EECs (maximum/average), LC50/LD50 (lowest value available), NOAEC (lowest value available) or using surrogate data (Kenaga monograph) instead of endosulfan specific data is not appropriate and does not reflect the real life picture. This evaluation needs modifications using more probabilistic assessments.

Page 19,

EPA comment: *Table 11*

ETF Response: The use of the maximum label rates (instead of e.g. "typical" rates) for calculating acute risk quotients is not a "non-conservative" approach as claimed in other parts of the document.

Page 21,

EPA comment: *Table 14*

ETF Response: The used crop application rates and numbers are not correct for lettuce (label states 1 lb./A, 3 applications) instead of 1.5 at 2 applications. For potatoes the label states 1 lb/A at 3 applications instead of 3 lbs/A once. The change of these input parameters will effect the results of the acute and chronic RQs.

Page 21

EPA comment: *"…the use of buffers does not reduce the likelihood of exceeding either acute or chronic LOCs"*

ETF Response: This statement should be changed. As outlined in several responses above, buffer zones will also reduce runoff, significantly. As a consequence EEC values will be significantly lower with a concomitant decrease in risk quotients. Therefore, the likelihood of exceeding acute or chronic LOCs will be reduced, as outlined in ETF's submitted risk assessment (MRID# 44903601).

Page 23,

EPA comment: *Table 15*

ETF Response: The use of PRZM/EXAMS is not appropriate to calculate EECs for the estuarine/marine environment.

Page 22,

EPA comment: *Table 15*

ETF Response: The used crop application rates and numbers are not correct for lettuce (label states 1 lb./A, 3 applications) instead of 1.5 at 2 applications. For potatoes the label states 1 lb/A at 3 applications instead of 3 lbs/A once. The change of these input parameters will effect the results of the acute and chronic RQs.

Page 22,

EPA comment: *Table 15*

ETF Response: The LC50 of 0.1 µg/L for Striped Bass is taken from an "invalid" study. It would be more appropriate to use a value from an acceptable (core or supplemental study), e.g. the Striped Mullet LC50 of 0.38 µg/L (MRID#40228401). As a result all listed acute and

chronic RQs would change, if a more appropriate EEC was calculated (see earlier comment about the use of PRZM/EXAMS).

Page 23,

EPA comment: *Table 15*

ETF Response: The LC50 of 0.1 µg/L for Striped Bass is taken from an invalid study. It would be more appropriate to use a value from an acceptable (core or supplemental study), e.g. the Striped Mullet LC50 of 0.38 µg/L (MRID#40228401). As a result all acute and chronic RQs would change, if an acceptable EEC could be calculated (see earlier comment about the use of PRZM).

Environmental Risk Characterization

Page 23

EPA comment: *"Based on a non-conservative screening level assessment using typical application rates…"*

ETF Response: Worst case assessments (highest label rates and shortest intervals) were used for the terrestrial assessment including surrogate plant residue data instead of endosulfan specific field data. Thus the wording "non-conservative" is not correct and should be deleted. Concerning the aquatic risk assessment, the assessment still does not represent a "non-conservative" or "typical" scenario (see the use of the 300ft. buffer, used only as a drift and not runoff buffer; use of most sensitive species with lowest available effect value, even if studies are invalid).

Page 23

EPA comment: *"Environmental monitoring studies confirm widespread contamination of surface water."*

ETF Response: This sentence should be deleted, since a "widespread" contamination is NOT confirmed if all data are properly evaluated.

Page 23

EPA comment: *"Incident data also confirm EFED's expectation that endosulfan's current use represents a serious risk"*

ETF Response: This statement is misleading. All the incidents irrespective of the causes (Registered Use, or Misuse, or N/R) were analyzed together. However, EPA's conclusions from that were drawn towards the registered use of endosulfan. The available incident database, especially for California, indicates that the number of incidents from registered endosulfan uses has significantly decreased.

Page 23

EPA comment: *"…conduct a more refined risk assessment that was based on actual reported application rates in California coupled with a 300-ft spray-drift buffer"*

ETF Response: The 300 ft buffer also impacts runoff, which needs to be considered in the calculation of EECs.

Page 23

EPA comment: *"…monitoring studies confirm widespread contamination of surface water…"*

ETF Response: The sentence is incorrect and should be deleted. . The surface water monitoring results after the introduction and implementation of use restrictions (between 1988 and 1993) show significantly lower concentrations of endosulfan residues in surface water and are well below the contamination level (MCL) – See Appendix 1. The results of analysis of surface water monitoring databases (STORET, USGS-NAWQA and CA-DPR) show no evidence of "widespread contamination".

Page 23

EPA comment: *"Based on the available toxicity data, incident data and a refined risk assessment, endosulfan represents a high acute risk to aquatic organisms."*

ETF Response: The sentence should be deleted or modified. While the toxicity data may indicate a high hazard, neither the incident data (after the time rate reductions and label changes including mitigation measures were in place) nor a truly refined risk assessment (c.f. assessment by Task Force, which was submitted in Oct. 1999, but not considered) indicate a high risk.

Page 23

EPA comment: *"…the assumptions for this assessment are not particularly conservative."*

ETF Response: This part of the sentence should be deleted. As the runoff buffer was not considered, PRBEN numbers were unrealistically low, laboratory soil dissipation rates were used and degradation rates from aerobic aquatic/sediment studies were ignored, the assessment is still a conservative one.

Page 23

EPA comment: *"Given that chronic risk quotients are several orders of magnitude greater than acute values, endosulfan's capacity to act as an endocrine disruptor…"*

ETF Response: The last part of the sentence should be deleted. Only in-vitro studies indicate a low affinity of endosulfan to the endocrine receptors. In-vivo studies including a vitellogenin study in fish indicate that there is no endocrine disruption by endosulfan (Heusel, 1999; MRID# 45218801). A more detailed response can be found below responding to Appendix K.

Page 23

EPA comment: *"Furthermore, a comparative risk assessment of endosulfan and 5 other chemicals (esfenvalerate, imidocloprid, dimethoate, methomyl and spinosad) considered to be alternatives, endosulfan rated as the most likely to pose the greatest overall risk to birds and aquatic organisms."*

ETF Response: The comparative risk assessment should be deleted. The selection of competitor products seems arbitrary. Data input and assumptions are not transparent. The assessment performed does not take into account the full label restrictions on endosulfan. Neither a comparison of the full pest spectrum controlled by the competitors' products with the spectrum controlled by endosulfan, nor the uses of endosulfan in IPM were considered.

The computer model used for the comparison (DecideRight®) is a model for business decision. Its use in comparative risk assessment has not been validated.

The SAP provided the following responses regarding the comparative risk assessment paradigm (Dec. 8-9, 1998):

"Panel members believe there are too many scientific uncertainties in the approach to allow one to assume that the results do more than provide a rough estimate of relative, not absolute, risk within a narrow class of pesticide uses. The validity and use of the proposed approach (or a portion thereof) depends on the intended use of the results. It was not clear to the Panel how the proposed approach would be used within the existing regulatory framework. Therefore, it was difficult for the Panel to answer the specific questions below without knowing exactly how the calculations will be used and without having a clear statement of the limitations and assumptions that went into the risk calculations."

"Several members of the Panel believe that comparisons of relative risk by simple combinations of RQs may not be meaningful."

"As detailed below, the Panel believes there are too many scientific uncertainties in the approach to allow one to assume that the results in fact quantify the true ecological risk. In addition, the assumption that all products are interchangeable is not always true."

Page 23

EPA comment: *"…likelihood of ecological effects is based on surrogate species…" "The sensitivity of the surrogate species may not however, be representative of the most vulnerable organisms."*

ETF Response: The use of "surrogate species" is standard practice in all ecotoxicological testing and risk assessment. For this reason EPA uses safety factors (or Levels of Concern) in the calculation of Risk Quotients. The reference to the sensitivity of the surrogate species should be deleted.

Page 23

EPA comment: *"it remains uncertain whether the full distribution of effects has been captured."*

ETF Response: The reference to the uncertainty should be deleted. The unusual high number of available study results for Endosulfan with a large number of species, especially in the aquatic environment provides a solid basis for the risk assessment.

Page 24

EPA comment: *"…endosulfan-related incidents account for the greatest percentage of nontarget mortality reported in EPA's Ecological Incident Information System"*

ETF Response: This statement is incorrect and should be deleted. The statement would be only true if values are included before the application rate reduction and label changes including mitigation measures (see 300 ft. buffer) were in place (1987 – 1994, see Appendix 1).

Page 24

EPA comment: *"Although incident reports confirm the likely acute effects that EFED expects…"*

ETF Response: This sentence is incorrect and should be deleted. Incidents mainly occurred before the rate reduction and label changes including mitigation measures were in place (1987 – 1994, see Appendix 1); especially if one considers the 33% (29) of the total incidents in California occurred since 1971. Out of the 29 reported cases 20 were recorded in the '70s, 5 in the '80s and 4 in 1996. Only one of the four reported incidents in 1996 was caused by the registered use of endosulfan, the other three were either misuse or the cause could not be identified. This trend clearly shows that the California mitigation measures as enforced by permit restrictions in the late 80s, and consequently incorporated on the ETF product labels (officially approved in April 1992) are effective and demonstrate that the use of Endosulfan under those conditions is safe.

Page 24

EPA comment: *"…chronic RQ values ranging as high as 680…"*

ETF Response: The value of 680 is wrong. Even if based on the draft RED, the highest value is 487, and this value (Table 15) is based on a study rendered "Invalid" by EPA. Similarly, the ETF contests the exposure estimates, which if considered would further reduce risk quotients.

Page 24

EPA comment: *"Given the reproductive and developmental effects of endosulfan, coupled with the chemical's ability to bind to the human estrogen receptor, these chronic effects could have a considerable impact on nontarget organisms."*

ETF Response: This sentence should be deleted. In the HED Risk Assessment for Endosulfan RED document (Barcode D250471, 2/17/00), it was stated that HED has thoroughly evaluated data on the developmental and reproductive toxicity of endosulfan in mammals. HED determined that endosulfan was not a developmental or reproductive toxicant, and concluded: *"The data base is complete and there are no data gaps pertaining to developmental or reproductive toxicity. The data provided no indication of increased sensitivity of rats or rabbits to in utero and post-natal exposure to endosulfan."* Based

on the complete database, HED stated again, in the Executive Summary, that *"Results from development and reproductive toxicity studies conducted under OPPTS guidelines do not show increased or special sensitivity of the fetus or offspring to the toxicity of endosulfan"*

While endosulfan has been shown to have very weak estrogen binding potential in in vitro screening assays, scientific groups such as the Endocrine Disrupting Screening and Testing Advisory Committee (EDSTAC) and the OECD Task Force for Endocrine Disrupter Testing and Assessment (EDTA) have emphasized that this type of screening data has limited predictive capabilities. Therefore, before a definitive finding of endocrine disruption can be made, evaluation through in vivo screening and testing must be conducted and a weight-of-evidence determination concluded from all available data. In addition, the data cited used assays that have been determined to be too unreliable for regulatory screening purposes, and the results have not been supported by data generated from a multitude of valid in vivo screening and testing methods. As stated by HED, until EPA has completed development of criteria for the evaluation of endocrine disruption, classification of a chemical as an endocrine disrupter is scientifically inappropriate. The ETF strongly believes that a full evaluation of available data for endosulfan will clearly show that endosulfan is not an endocrine disrupter. Therefore, until EPA has fully evaluated all relevant data and argumentation, and until the criteria are established for classifying a compound as an endocrine disrupter, a reference to an alleged endocrine disruption potential is inappropriate, misleading and should be deleted.

Page 24

EPA comment: *"Environmental monitoring studies demonstrate widespread contamination of surface…"*

ETF Response: This allegation should be deleted. The surface water monitoring results after the introduction and implementation of use restrictions (between 1988 and 1993) show significantly lower concentrations of endosulfan residues in surface water and are well below the contamination level (MCL). A detailed analysis is presented in Appendix 1.

Page 24,

EPA comment*: "With repeated applications in the same year, or even in consecutive years, concentrations of endosulfan and endosulfan sulfate may build up in the soil."*

ETF Response: From monitoring studies (Tiirmaa & Dorn, 1988) covering different geographical areas and environmental conditions it can be concluded that endosulfan does not accumulate or form a concentration plateau of ecotoxicological relevance in soils even after extensive and consecutive use for several years under normal agricultural practices. The report will be submitted by the ETF.

Page 24

EPA comment: *"Endosulfan has been detected in nearly all environmental compartments, including surface- and ground-water and in areas where it is not used (e.g., the Arctic, mountains of California, and national parks). The widespread nature of endosulfan contamination*

is evident in the STORET data base, which reports detects of one or more endosulfan residue in 38 states."

ETF Response: The statement is misleading. The allegation should be deleted; see same argumentation applies as presented above.

Page 25

EPA comment: *"A single application at 1 lb a.i./A (lower than maximum label rates) is likely to result in acute high risk to both terrestrial and aquatic organisms. Additionally, the current use rates for endosulfan are expected to result in chronic toxicity to both terrestrial and aquatic nontarget organisms."*

ETF Response: The assessment of "high risk" should be deleted as it is only based on unrealistic assumptions disregarding e.g. runoff buffers. Refer to risk assessments submitted by ETF (MRID# 44953102, 44953103, 44953104).

Page 25/26

EPA comment: *Study requests numbering*

ETF Response: The requests should be numbered starting with "1" instead of "17"

Page 25/26

EPA comment: *Study requests*

ETF Response: see commentary to the study requests above (Task Force Response to the Data Gaps Listing as Identified by EFED).

Page 26

EPA comment: *"RQ values will exceed the acute high risk LOC is greater than 99% for seven out of the eight modeled crops…"*

ETF Response: The RQ calculations should be modified reflecting realistic conditions.

Page 26

EPA comment: *"Incidences"*

ETF Response: The last paragraph referencing non-US incidents should be deleted. The use patterns, and backgrounds for these incidents may not relate to the conditions in the US, both from a practical use and awareness standpoint. Additionally, as with all incidents, the reporting of such in a paper does not necessarily mean that the effects reported were actually caused by endosulfan, but only that the author may have made a connection.

Page 27

EPA comment: *"Thus, while the EIIS may not reflect an unbiased estimate of incidents, minimally it is useful for documenting ecological field effects that substantiate EFED concerns about nontarget mortality."*

ETF Response: This statement is disputable; the sentence should be deleted. That statement would only be correct if the incidents cited indeed would have been caused by endosulfan under normal use conditions. As even EPA states that the EIIS may not reflect an unbiased estimate, the reference is only a weak proof.

Page 27,

EPA comment: *"result of intentional misue"*

ETF Response: Typographical error: "result of intentional misuse"

Page 27/28

EPA comment: *"It is also significant to note that fish kill incidents have continued in the remaining states since a 300-ft spray-drift buffer was added to endosulfan technical labels. Thus, despite use restrictions to limit degradation of the aquatic environment, endosulfan has continued to access the aquatic environment and result in nontarget mortality."*

ETF Response: After the change in application rates and incorporated label mitigation measures (especially in California), the incident database does not confirm EPA's statement.

Page 28

EPA comment: *"According to the National Oceanic and Atmospheric Agency's fish-kill database (Pait et al, 1992), endosulfan was responsible for more fish kills in U.S. estuaries and coastal rivers between 1980 and 1989 than all currently used pesticides at that time."*

ETF Response: Most of the reported fish kills occurred before rate reductions and label changes including mitigation measures were in place. Thus the reference should be deleted.

Page 28

EPA comment: *"Additionally, monitoring of endosulfan residues in mussels (Wade et al. 1998)…"*

ETF Response: This reference needs at least a qualifying statement. The author states "*The two components endosulfan I and II are not always chromatographically resolved from other analytes with the methods used in this study and therefore their detections at low concentrations was not reliable.*"

Page 28

EPA Comments: *Mutagenicity – Based on the results of sex-linked recessive lethal (SLRL) and sex chromosome loss (SCL) tests on fruit flies (Drosophila melanogaster), endosulfan has been demonstrated as a mutagen in insects (Velazquez et al. 1984). The mutagenic effect of endosulfan has also been linked to blood cell changes observed in mammals (Sylianco 1978; Usha Rani et al. 1980).*

ETF Response: Endosulfan is not mutagenic in mammalian cells. HED evaluated the available data for endosulfan for mutagenic potential and concluded the following: "*Endosulfan was not carcinogenic and did not show **any*** [emphasis added] *mutagenic potential. There was no increase in the frequency of tumors in either the rat or mouse carcinogenicity studies. Endosulfan is classified as a Group E carcinogen (evidence of non-carcinogenicity for humans) by the Agency. The submitted mutagenicity studies have satisfied the data requirements for mutagenicity testing, and there is no concern for a mutagenic effect in somatic cells. In the in vitro or in vivo mutagenicity studies, both the mouse lymphoma forward mutation assay and the unscheduled DNA synthesis assay were negative*" (P. 3 HED Toxicology Chapter for the RED). In addition, hematological effects noted in subchronic and chronic studies were secondary to the direct cytotoxic effect of endosulfan on the liver and spleen, and were not associated with genotoxicity. HED determined that the guideline data is complete, reliable and conclusive, clearly showing that endosulfan is not mutagenic in mammalian cells. Therefore, while data from public literature should be acknowledged and evaluated for scientific merit, the implication that this data is conclusive is misleading and inappropriate. The ETF respectfully request that this statement be removed or that HED's conclusions be included in the discussion of mutagenicity for endosulfan. The ETF also recommends that all available data on mutagenicity in non-mammalian species be evaluated prior to making a final determination. Using a single reference to a non-guideline study, without evaluation of the entire database, is scientifically inappropriate.

Page 29,

EPA Comment: *Endocrine Disruption – Exposure to endosulfan has resulted in both reproductive and developmental effects in non-target animals (Appendix K). Amphibians exposed to endosulfan exhibited impaired development of tadpoles into adults (Berrill et al. 1998). In birds, endosulfan impaired the development of the genital tract (Lutz and Lutz-Ostertag 1975). In mammals, endosulfan reduced hormone levels (Wilson and LeBlanc 1997), produced testicular atrophy (NCI 1978; Gupta and Gupta 1979) and reduced sperm production (Dalsenter et al. 1999). Additionally, endosulfan has been demonstrated to bind to the human estrogen receptor and exhibit significant estrogenic activity at concentrations as low as 10^{-6} M (Massaad and Barouki 1999; Ramamoorthy et al. 1997; Soto et al. 1995). Whether the toxicity endpoints observed during chronic toxicity studies reported in this chapter are a result of endocrine disruption is not known. However, it is clear that organisms treated with endosulfan did exhibit some toxic effects that have historically been associated with endocrine disrupting chemicals, e.g., developmental and reproductive effects (Ankley et al. 1998).*

ETF Response: As these arguments were provided in further detail by EFED in Appendix K, please refer to the ETF response for Appendix K.

Page 30

EPA comment: *"However, incident data suggest that under certain conditions endosulfan is phytotoxic."*

ETF Response: While EPA proposes that *"incident data suggest phytotoxicity under certain conditions"* the database does not provide more information if lettuce was both the application target and the species affected. The listing in the incident database only constitutes a claim, but no established cause and effect. Effects may have been caused e.g. by insufficiently cleaned spray equipment after herbicide application. Until more details of these incidents are known, the sentence should be deleted.

Page 30

EPA comment:

1. "*the Agency has proposed endosulfan as a candidate for the development of a National Action Plan under the PBT strategy…" ." the available Octanol/Water partition coefficient, Kow, and the Bioaccumulation factors available suggest a high bioaccumulation potential for endosulfan.*"

2. "*Overall, the Kow and BDF values point to a relatively large potential for bioaccumulation for endosulfan and its residues*"

ETF Response: The reference to the PBT strategy is not necessary for the assessment, misleading, and should be deleted. Endosulfan is not included in the two recent listings by EPA related to PBT chemicals (Final rule published on October 29, 1999 in Federal Register) and the Press Advisory published on August 31, 2000 regarding EPA PBT Initiative).

Endosulfan was included in the "*proposed*" list, for comments, by EPA/RCRA under the "Draft RCRA Waste Minimization PBT chemical List". As evident in the contents of the Federal Register Notice (11/9/98), the RCRA inclusion is solely based on a partial database of laboratory values (K_{OW}, BAF/BCF), and the use of these laboratory numbers to derive the justifying "*scores*" by the use of a computer modeling software (WMPT). Such approach ignores all other available ecobiology and environmental data conducted under actual field conditions. Collectively, these data show clearly that endosulfan does not bioaccumulate or persist in the active soil environment under actual agricultural and field conditions. ETF has since responded to the RCRA proposal and had provided the Agency with a complete data summary including those from worldwide field-testing. Endosulfan was not listed as a result of considerations of realistic conditions.

It is apparent that EFED did not consider the statements contained in other sections of the review where rapid depuration of observed bioaccumulated residues in the relevant studies was cited. Therefore, the Agency should delete the reference to PBT or add a qualifying statement like "*However, depuration studies conducted in fish suggest that endosulfan residues do not bioaccumulate under natural conditions*".

Page 31

EPA comment: *Refined Risk Assessment and Characterization*

ETF response: ETF appreciates the efforts of EPA to refine the Tier II exposure assessment and considering more realistic assumptions. However, one of the assumptions of considering

the effect of the 300-foot buffer only for spray drift reduction is not realistic. In addition, in the PRZM/EXAMS modeling a number of sensitive parameters chosen by EPA are unrealistic and inappropriate:

- In the cotton scenario the curve numbers used were inappropriate. A curve number of 99 would yield higher runoff than from a farm road (PRZM manual Curve Number Table).
- PRBEN value of 0.5 for a compound like Endosulfan (having a high Koc) is inappropriate (0.9 should be used instead). If there is any relevant recent literature available as stated by the EPA addressing this issue, it should be quoted in the document.
- Aerobic Aquatic Metabolism Half-Life: EPA assumed aerobic aquatic half-life to 2 times the aerobic soil half-life (114 days for α-endosulfan and 416 days for β-endosulfan). This is not correct particularly for endosulfan, which is readily hydrolyzed in water. The aerobic aquatic studies submitted by the ETF (MRID: 44917801 and 44917802) was deemed as a supplementary study by the EPA. Therefore, the degradation rate (T½ for α- and β-endosulfan = 12 to 15 days and for total α-, β- and endosulfan-sulfate = 18 to 21 days) in the total sediment/water system from the above study should be used in the PRZM/EXAMS modeling. Using the correct values would produce significantly lower (acute and chronic) concentrations of endosulfan residues in the receiving water.

Due to these limitations with the exposure assessment conducted by EPA does not reflect realistic worst case scenarios and the results from the assessment are not appropriate to be used in further risk assessment. ETF submitted a refined exposure assessment including the influence of buffers on runoff and erosion losses (MRID# 44953103). ETF respectfully requests the EPA to use the results from this exposure assessment for their risk assessments.

Page 31

EPA comment: *"…the assessment EFED used included several non-conservative assumptions,…"*

ETF Response: While some of the parameters may be regarded non-conservative, other parameters (e.g. exclusion of the impact of a buffer zone for runoff) are still conservative (Refer to above response from ETF).

Page 31

EPA comment: *"…striped bass (0.1 μg/L)…"*

ETF Response: The striped bass value should not be used as it is taken from a study rated "Invalid" by EPA (see above).

Page 31

EPA comment: *"…corresponding application rate was back calculated using PRZM/EXAMS."*

ETF Response: The use of PRZM/EXAMS is inappropriate for the calculation of concentrations in the marine/estuarine environment.

Page 32,

EPA comment: *Table 16*

ETF Response: The highest single application label rate for lettuce is 1.0 lb a.i./Acre

Page 32

EPA comment: *" However, had the most sensitive fish species (i.e., stripped bass), been used to estimate risk quotients, …"*
" However, similar to lettuce, if LOCs were based on the acute mortality estimate for stripped bass, …"

ETF Response: The striped bass value should not be used as it is taken from a study rated "Invalid" by EPA. (also typographical error "stripped bass " instead of "striped bass".)

Page 33,

EPA comment: *Table 17*

ETF Response: Some of the values reported are incorrect. The highest seasonal application rates are e.g. for grapes up to more than 10 times (33 lb a.i./A) of the maximum allowable seasonal label rate. Also the lowest reported rates (lettuce 0.03 lb/acre) are below any effective (and recommended label) application rate.

Page 33 ff

EPA comment: *(EEC graphs of use and distribution)*

ETF Response: The ETF exposure assessment using realistic use conditions and current label mitigation such as 300 ft buffer zones (MRID# 44953102 – 04) shows that endosulfan poses a low risk to aquatic organisms. A more detailed response will be provided during the 60-day comment period.

Page 35

EPA comment: *"This phase of the refined assessment considers the probability of endosulfan affecting an aquatic system as a whole."*

ETF Response: This statement needs to be rephrased, as the selection of species (fish, some invertebrates) cannot represent an "aquatic system as a whole". The selected species are not only limited, but also are selected for the higher sensitivity. One must assume that the sensitivity of organisms in an aquatic system is distributed in a similar way as the sensitivity of the large number of test organisms spanning several orders of magnitude.

Page 35

EPA comment: *"This assumed universe comprised striped bass, pinfish, rainbow trout, flathead catfish, channel catfish, flathead minnow, bluegill sunfish, eastern oysters, blue crab, and fiddler crab."*

ETF Response: The striped bass value should not be used as it is taken from a study rated "Invalid" by EPA. Typographical error "flathead minnow" instead of "fathead minnow".

Comparison of modeling and monitoring

Page 36

EPA comment: ***(Comparison of modeling and monitoring)***

ETF Response: The range of monitoring data considered in the comparison includes data prior to the introduction and implementation of use restrictions (1990). Appendix 1 shows that in surface water monitoring records (STORET, NAWQA and CA-DPR Surface Water Database) show significantly reduced levels of the endosulfan concentrations in surface water after the introduction of use restrictions. The exposure concentrations estimated by EPA compare more closely with the monitoring data (STORET) data prior to the introduction of use restriction (1990), but not to the data after 1990 (Appendix 1). On the other hand, the exposure concentrations estimated by the ETF (MRID# 44953103) are generally higher than the monitored values, but are within realistic magnitude of the monitoring data after 1990. This further compels the necessity of considering the effect of buffer on runoff in the exposure estimations.

Summary and Conclusions

Page 37

EPA comment: ***(Summary and Conclusion)***

ETF Response: As a result of the comments presented above, the ETF respectfully requests the summary and conclusion section to be changed.

Page 37

EPA comment: *"However, adverse chronic impacts can be expected given that chronic risk quotients are several orders of magnitude greater than acute values and given endosulfan's capacity to act as an endocrine disruptor…"*

ETF Response: This section should be deleted. Endosulfan does not act as an endocrine disrupter in in-vivo studies. At this point, until EPA has fully evaluated all relevant data and argumentation, and until the criteria are established for classifying a compound as an endocrine disrupter, a reference to an alleged endocrine disruption potential should be deleted.

Comparative Risk Assessment

Page 38

EPA comment: *Comparative Risk Assessment*

ETF Response: The comparative risk assessment should be deleted. The selection of competitor products seems arbitrary. Data input and assumptions are not transparent. The assessment performed does not take into account the full label restrictions on endosulfan. Neither the full pest spectrum of the competitors nor the uses of endosulfan in IPM were considered.

The computer model used for the comparison (DecideRight®) is a model for business decision. Its use in comparative risk assessment has not been validated.

The Scientific Advisory Panel provided the following responses to the comparative risk assessment paradigm (Dec. 8-9, 1998)

"Panel members believe there are too many scientific uncertainties in the approach to allow one to assume that the results do more than provide a rough estimate of relative, not absolute, risk within a narrow class of pesticide uses. The validity and use of the proposed approach (or a portion thereof) depends on the intended use of the results. It was not clear to the Panel how the proposed approach would be used within the existing regulatory framework. Therefore, it was difficult for the Panel to answer the specific questions below without knowing exactly how the calculations will be used and without having a clear statement of the limitations and assumptions that went into the risk calculations."

"Several members of the Panel believe that comparisons of relative risk by simple combinations of RQs may not be meaningful."

"As detailed below, the Panel believes there are too many scientific uncertainties in the approach to allow one to assume that the results in fact quantify the true ecological risk. In addition, the assumption that all products are interchangeable is not always true."

Appendix A Supporting Environmental Fate Studies Submitted to the Agency

Page 44

EPA comment: *(Table A-2)*

ETF Response: It is not transparent how EPA calculated the half-lives. DT50 values calculated by the registrant differ from those listed in the table.

Page 45

EPA comment: *(Half-lives in first paragraph)*

ETF Response: The cited half-lives need to reflect the above mentioned revisions.

Page 47

EPA comment: *"Extractions of the soil do not appear to be exhaustive."*

ETF Response: This statement should be deleted. Triplicate extractions in the extraction scheme seem to have not been noticed in the evaluation of the study.

Page 48

EPA comment: *"(Mobility for Endosulfan Degradates)"*

ETF Response: A study is missing (MRID# 41412905), the results of which are in agreement with the K_{OC} calculations presented on page 3, Table 1.

Page 49/50

EPA comment: *(Georgia Tomato/Soil Study (MRID 413097-02))*

ETF Response: As stated in our comments to Table 2 the values for α-endosulfan, β-endosulfan, and sulfate are wrong and should be corrected.

Page 50/51

EPA comment: *(California Cotton/Soil Study (MRID 414686-01))*

ETF Response: As stated in our comments to Table 2 the values for α-endosulfan, β-endosulfan, and sulfate are wrong and should be corrected.

Page 53

EPA comment: *(Runoff)*

ETF Response: The results of the South Carolina runoff study (MRID# 41309701, Mester, 1989), which actually had a 200ft. vegetative buffer, as well as the Farm Pond study without a buffer (MRID#41164101; Cornaby,1989) are not presented in this chapter. The S. Carolina study was reviewed by the Agency (1/11/93; H. Nelson) and considered technically strong in many ways, but not sufficient to fulfill the guideline requirement, mainly because of the chosen soil type, application technique (aerial instead of ground) and slow irrigation rate. The pond study was reviewed (4/24/91; N. Cook) and found acceptable.

Page 54

EPA comment: *"...with bioconcentration factors of 2,429 for edible tissue…"*

ETF Response: The accumulation factor for edible tissue should be 2249 instead of 2429. It also should be added that there was no detection of residues after 48 h of depuration.

Appendix B Fate and Transport

Page 57

EPA comment: *"The structural differences and conversion between the two isomers are important in understanding the fate processes and estrogenic effects of endosulfan in relation to endocrine mimic activity and binding (Soto, 1994)."*

ETF Response: This second part of the sentence should be deleted. Alleged estrogenic effects, especially if not true, should not be part of fate and transport discussions.

Page 57

EPA comment: *(Environmental Fate Characteristics)*

ETF Response: The presentation of toxicity values in the context of environmental fate discussions is misleading and should be deleted.

Page 57/58

EPA comment: *(Table B-1 and B-2)*

ETF Response: The physico chemical properties presented by Montgomery (1993) and McConnell et al (1998) are a secondary source of information (i.e. not original papers), and as such should not be quoted.

Page 60

EPA comment: ***"****Dying plant tissues were believed to be a source of slow release of endosulfan back into the pond microcosm."*

ETF Response: This statement should be deleted. Barry and Logan (1998) speculated: "*Dying plant species may have also been an important source for the slow release of endosulfan back into the microcosms*", but did not offer any proof. The release of absorbed endosulfan from dying macrophytes was not investigated in this study. The concentration of endosulfan measured in the microcosms follows a smooth decline pattern and did not suggest slow release into water phase from any adsorbed source. The study notes that only 6 to 12 % of the applied endosulfan (as endosulfan and endosulfan sulfate) was present in the macrophytes at the end of the study. The study also notes that metabolism of endosulfan in the macrophytes and algae as significant route of degradation. Therefore, if there is a potential for endosulfan to be released back into water upon dying of macrophytes, the amount that will be available for release will be what is left from degradation in the macrophyte tissue and will be infinitesimal.

Page 60

EPA comment: (*Environmental Monitoring, Atmospheric Transport)*

ETF Response: Additional important publications need to be considered for this chapter (Bidleman et al.,1990, Organic Contaminants in the Northwest Atlantic Atmosphere at Sable Island,1988-1989, Chemosphere;1992,p.1389-1412; Hoff et al.,1992; Annual Cycle of Polychlorinated Biphenyls and Organohalogen Pesticides in Air in S. Ontario; Environm.Sci.Technology;1992,26;2; 166-175; Simonich&Hites,1995; Global

Distribution of Persistent Organochlorine Compounds; Science;1995;269; 1851-1854. Based on these publications Endosulfan is detectable only in very low concentrations in the air during the time of application and decreases to extremely low levels during off-season. The extremely low traces occasionally found in remote areas were not confirmed in every reported case.

Page 62/63

EPA comment: *(Table B-7)*

ETF Response: All of the reported values for Endosulfan in surface waters (see Table B-7) are below the reported limit of detection (<5 ppt), which should be a definite value (not "less than"). The limit of quantification and detection for the total method (including SPE) are not reported.

Page 64

EPA comment: *"…concentrations ranging from 9 to 89 ng/g (Wade et al, 1998)"*

ETF Response: This reference needs at least a qualifying statement. The author states "*The two components endosulfan I and II are not always chromatographically resolved from other analytes with the methods used in this study and therefore their detections at low concentrations was not reliable.*"

Page 64 Florida Bay Joe Bay (FL)

EPA comment*: The authors noted that while endosulfan is reported to have been responsible for more fish deaths in US estuaries and coastal waters between 1980 and 1989 than any other currently-used pesticide, analytical measurement problems make quantification of endosulfan difficult.*

ETF Response: The reference should be deleted. The statement is a contradiction in itself by stating that endosulfan was responsible for fish kills, while its analytical quantification is difficult.

Page 64

EPA comment: *"Outside the United States"*

ETF Response: This paragraph should be deleted. The relevance of findings outside US is questionable as use conditions, methods and awareness of environmental contamination differ greatly. An anecdotal reporting creates the impression of evidence, while the selection of the monitoring data is arbitrary.

Page 64/65

EPA comment: (*Groundwater, Table B-9)*

ETF Response: The reference to a Spanish groundwater monitoring report is inappropriate and should not be used for an US EFED assessment. The circumstances of the findings are not known. Use conditions and environmental awareness are different from the conditions in the US.

Appendix C

Page 68

EPA comment: *(PRZM and EXAMS parameters)*

ETF response: A number of sensitive parameters chosen by EPA in their exposure assessment are unrealistic and inappropriate.

- In the cotton scenario the curve numbers used were inappropriate. A curve number of 99 would yield higher runoff than from a farm road (PRZM manual Curve Number Table).

- Instead of a PRBEN value of 0.5 for a compound like Endosulfan (having high Koc) a value of 0.9 is more appropriate. If there is any relevant recent literature available as stated by the EPA addressing this issue, it should be quoted in the document.

- Aerobic Aquatic Metabolism Half-Life: EPA assumed aerobic aquatic half-life to 2 times the aerobic soil half-life (114 days for α-endosulfan, and 416 days for β-endosulfan). This is not correct particularly for endosulfan, which is readily hydrolyzed in water. The aerobic aquatic studies submitted by the ETF (MRID: 44917801 and 44917802) was deemed as a supplementary study by the EPA. Therefore, the degradation rate (T½ for α- and β-endosulfan = 12 to 15 days and for total α-, β- and endosulfan-sulfate = 18 to 21 days) in the total sediment/water system from the above study should be used in the PRZM/EXAMS modeling.

Page 68

EPA comment: *(Table C-1)*

ETF response: Aerobic Aquatic Metabolism Half-Life: See above.

Spray Efficiency: Table C-1 states spray efficiency as 75 %. However, the model input files have spray efficiency as 99 %. ETF used 95 % as spray efficiency in its exposure assessment (MRID# 44953103)

Spray Drift: In Table C-1 spray drift is mentioned as 5 % of applied. However, the input files indicate 0 % due to the presence of the 300-ft buffer.

Appendix E Ecological Studies

Page 89,

EPA comment: *Table E-7*

ETF response: Rainbow Trout (MRID# BA007902), the indicated % ai of 86 must be an error; usually the technical material is 96% a.i.

Page 90,

EPA comment: *Table E-7*

ETF response: Macek et al (1976) report the LC_{50} of 0.86 µg/L for the fathead minnow (*Pimephales promelas*) and not for a flathead catfish (*Pylodictis olivarius*) as stated in the table.

Page 90,

EPA comment: *3 lines above Table E-8: "formulationof"*

ETF response: Typographical error: "formulation of"

Page 90,

EPA comment: *Table E-8*

ETF response: In the presentation of the formulation data it should be made clear if the results refer to total product (formulated) or a.i. (technical)

Page 92,

EPA comment: *"It is noteworthy that the LOEC estimate for daphnids is equivalent to the acute toxicity estimate (6 µg/L) for scuds and does not provide a meaningful estimate of the chronic toxicity for freshwater invertebrates. Regression analysis of the 50-day survival data suggests that, the NOEC could be estimated at 2.0 µg/L Although the study (MRID 5008271) was initially classified as core, the study fails to provide an estimate of the NOEC and has been reclassified as supplemental. However, assuming the estimated NOEC of 2.0 µg/L is an accurate estimate of the NOEC for daphnids, then the acute to chronic ratio for daphnids (LC_{50}/NOEC: 166/2) could be used to predict the NOEC for the most sensitive species, i.e., scuds. The result of this calculation is a predicted NOEC of 0.07 µg/L for scuds. The chronic invertebrate toxicity testing requirement (Guideline 72-4) is not fulfilled."*

ETF response: The chronic daphnia reproduction study is being re-classified in the text of the review. In Table 11 it is still classified as "core". The DER is needed to properly assess the reclassification and the statement that the requirement is (now) not fulfilled.

Page 92,

EPA comment: "…*striped bass (Morone saxatilis) were the most sensitive (LC_{50} = 0.1 µg/L) species tested."*

ETF response: The values for the Striped Bass (0.1 ppb acute and 0.01 ppb chronic) should be deleted, as it results from a study that is rated "INVALID; temperature fluctuations too great" in the reference list on page 108. The more appropriate study to cite here is for the Striped Mullet (LC50 = 0.38 ppb; see p.93; MRID# 40228401, this study is classified as core)

Page 92,

EPA comment: *(Table E-12)(Striped Bass is classified "supplemental"*

ETF response: The reference of the Striped Bass should be deleted, as it results from a study that is rated "INVALID; temperature fluctuations too great" in the reference list on page 108.

Page 93,

EPA comment: *" ... based on the most sensitive marine species tested, i.e., striped bass (LC_{50} = 0.1 µg/L)"*

ETF response: The values for the Striped Bass (0.1 ppb acute and 0.01 ppb chronic) should be deleted, as it results from a study that is rated "INVALID; temperature fluctuations too great" in the reference list on page 108. The more appropriate study to cite here is for the Striped Mullet (LC50 = 0.38 ppb; see p.93; MRID# 40228401, this study is classified as core).

Page 93/94

EPA comment: *Table E-12, E-13, and E-14*

ETF response: The reference Mayer (MRID# 40228401) is not contained in any reference list.

Page 94

EPA comment: *Table E-16*

ETF response: A reference should be provided for the Eastern Oyster.

Page 95

EPA comment: *" Suitability of Ecotoxicity Data Submissions"*

ETF response: Inconsistencies between the text, the classification of the studies and the reference list should be checked. For instance, the reference for acute toxicity studies by "Hudson et al." is cited with a MRID number of 160000 as "*core*" in Table E-1 on page 86. However, this reference is not contained in Table E-17 "*Studies, classified as acceptable, that were submitted to support the reregistration of Endosulfan*", but in Table E-18 "*Studies that were submitted to support the reregistration of Endosulfan but did not pass initial screen. Data discrepancies responsible for rejection are listed"* with the MRID number 05003462 and the comment "insufficient data". In the reference list on page 110 the study is classified as "supplemental, upgradable".

Page 96

EPA comment: *reference 16* "*Fishcher*"

ETF response: The author of reference 16 should be "Fischer"

Appendix F Ecological Risk Assessment

Page 123 - 128

EPA comment: *(estimated environmental concentrations)*

ETF response: Instead of theoretical calculations based on Hoerger & Kenaga modified by Fletcher actual residue values should be used. The ETF submitted in 1987 (MRID# 40261301) a risk evaluation of Endosulfan to avian species including product specific plant residue data and its crop specific half-lives (123 trials on 18 different crops). This response was submitted in support of the revised maximum label rate (3 lbs./A/year). Assuming a NOEL of 30 ppm (Mallard Duck Reproduction) and given the crop specific half-lives (2.2 to 4.5 days) of total Endosulfan measured at day of application (93 ppm) and two weeks thereafter (0.5 ppm) indicates that the risk to terrestrial organism is acceptable.

Page 125

EPA comment: *4 lines above table F-6: "acture"*

ETF response: Typographical error: "acute"

Page 125

EPA comment: *Table F-6:*

ETF response: The exponents for the acute risk are missing.

Page 125

EPA comment: "*Therefore, birds are more susceptible than mammals to both organophosphate and carbamates in general. Since endolsulfan does not present an acute risk to endangered birds, mammals are also presumed to be protected."*

ETF response: The last two sentences should be deleted. The reference to organophosphates and carbamates is irrelevant for endosulfan, and, if the calculations presented are correct, endosulfan does present an acute risk to birds.

Page 126

EPA comment: *Typographical error: "grainivore "*

ETF response: Typographical error: "granivore"

Page 129 - 134

EPA comment: *Table F-13a, F-14a, F-15a, F-16a, F-16b*

ETF response: The label rates for lettuce should be 1 lb a.i./Acre x 3 instead of 1.5 lb a.i./A x2, and for potatoes it should be 1.5 lb a.i./A x 2 instead of 3 lb a.i./A x 1.

Page 130

EPA comment: *Table F-13c*

ETF response: exponent "b" should be "c" in places

Appendix G: Summary of Incident Data

Page 135

ETF response: The presentation of the incident data is somewhat misleading because

- All the incidents irrespective of the causes (Registered Use, or Misuse, or N/R) were analyzed together. However, conclusions from that were drawn towards the registered use of endosulfan.
- In several plots of incident data for different States presented by EPA, the years without incidents are missing. This gives the impression that there were endosulfan-related incidents happening every year.

Appendix H: RQ distribution

Page 151

ETF response: The RQ distribution is based on exposure estimation conducted by EPA using unrealistic worst case assumptions. Refer to ETF comments for Appendix –C.

Page 157

EPA comment: "*Discussion of Results"*

ETF response: In the, the statement about the "wide range of effects" in line 4 is not quite correct. As Fig. I-1 shows affected species vs. concentration, the type of effects are not addressed. The sentence could only state a "large number of species" that are likely to be affected.

Appendix J: Comparative Risk Analysis

Page 161

ETF response: The comparative risk assessment should be deleted. The selection of competitor products seems arbitrary. Data input and assumptions are not transparent. The assessment performed does not take into account the full label restrictions on endosulfan. Neither the full pest spectrum of the competitors nor the uses of endosulfan in IPM were considered.

The computer model used for the comparison (DecideRight®) is a model for business decision. Its use in comparative risk assessment has not been validated.

The FIFRA Scientific Advisory Panel (SAP) provided the following responses to the comparative risk assessment paradigm (Dec. 8-9, 1998)

"Panel members believe there are too many scientific uncertainties in the approach to allow one to assume that the results do more than provide a rough estimate of relative, not absolute, risk within a narrow class of pesticide uses. The validity and use of the

proposed approach (or a portion thereof) depends on the intended use of the results. It was not clear to the Panel how the proposed approach would be used within the existing regulatory framework. Therefore, it was difficult for the Panel to answer the specific questions below without knowing exactly how the calculations will be used and without having a clear statement of the limitations and assumptions that went into the risk calculations."

"Several members of the Panel believe that comparisons of relative risk by simple combinations of RQs may not be meaningful."

"As detailed below, the Panel believes there are too many scientific uncertainties in the approach to allow one to assume that the results in fact quantify the true ecological risk. In addition, the assumption that all products are interchangeable is not always true."

Appendix K: Endocrine disruption

Page 170,

EPA comment: *Technical grade endosulfan and each of the α- and β-isomers were estrogenic at concentrations of 10 to 25 μM as measured in the E-screen test using Michigan Cancer Foundation human breast cancer estrogen sensitive cells (MCF-7 cells) (Soto et al. 1995). At concentrations of 2.5 x 10^{-5} M endosulfan resulted in a 4-fold induction in a yeast-based estrogenic response assay (Ramamoorthy et al. 1997). More recent in vitro studies (Massaad and Barouki 1999) have detected significant estrogenic activity of endosulfan at concentrations as low as 10^{-6} M. Although endosulfan's affinity for the human estrogen receptor is reported to be considerably lower than the endogenous estradiol (Heufelder and Hofbauer 1996), its ability to bind to the receptor at all renders the chemical capable of competing with the endogenous hormone and capable of eliciting hormone-like effects.*

ETF response: There is general scientific agreement that the *potential* of a chemical to cause endocrine disruption may be initially assessed using *in vitro* and *ex/in vivo* screening models. However, there are limitations to the predicitiveness of these types of assays, particularly the *in vitro* assays since they are incapable of replicating the intricacies of a biological system. *In vivo* screening models are more predictive, but also tend to focus on one or a few aspects, e.g. the uterotrophic assay mainly on uterus weight as a general measure for estrogenic activity. *In vivo* studies, where a functional endocrine system is present and the full interplay between normal physiological and biochemical processes occurs, provide the most definitive assessment of a chemical's potential for endocrine modulation. Studies that specifically evaluate sexual maturation, fertility and other reproductive endpoints, endocrine organ effects and generation-to-generation effects provide the most significant scientific evidence for regulatory purposes. Therefore, while the *in vitro* screening assays cited by EFED did show endosulfan to have very weak estrogen binding potential, these results are in no way deterministic of the actual endocrine potential of endosulfan in biological systems. In fact, data from several *in vivo* screening assays and toxicity studies were negative for endocrine activity for endosulfan.

The uterotrophic assay and the receptor binding studies published by Wade et al (1997) show that the slight estrogenic effects seen in vitro did not occur in vivo, even at sublethal doses. No effect on estrogen/androgen related activity as well as on thyroid

function was found. Three more uterotrophic assays have been published, each indicating a lack of endocrine effect at maximum tolerated doses. The results of these studies are significant since EPA and OECD are in the process of completing the validation of this assay for future regulatory screening purposes.

Table 1. Endosulfan: *In vivo* and *ex vivo* Estrogenic Assays

Type of *in vivo* study	Endpoints	Endocrine Effects
Competitive binding to rat uterus ER *ex vivo* (Wade et al. 1997)	estradiol binding to rER ‘	Endosulfan inhibits estradiol binding only at excess. The number of ER and PR in uterus was unchanged
Competitive binding to mouse uterus *ex vivo* (Shelby et al. 1996)	estradiol binding to mER	No competitive inhibition at 10^3 fold excess
Uterotrophic assay in sexually immature Sprague-Dawley rats (3 mg/kg/day i.p. on day 18-20 of age) (Wade et al. 1997)	Uterus: growth, peroxidase activity, number of PR/ER; Pituitary: weight, hormones (GH, prolactin, TSH, LH, FSH); Serum: Thyroxin	No uterotrophic activity or hormonal changes. DES caused increase in uterus weight (80%), peroxidase, prolactin and a decrease in number of ER
Uterotrophic assay in sexually immature CD 1-mouse (10 mg/ kg bw/day s.c. on days 17 -19 of age) (Shelby et al. 1996)	Uterine growth	No increase in uterine wet mass. DES, E_2, (4-OH)-tamoxifen, DDT, methoxychlor were positive
Uterotrophic assay in sexually immature AP-Wistar rats (5 - 100 mg/kg bw/day s.c. for 3 days) (Ashby et al. 1997)	Uterine growth	No increase in uterine wet mass. Estradiol and methoxychlor were clearly positive.
Uterotrophic assay on young ovariectomized female Wistar rats (Raizada et al. 1991)	Uterus / cervix / vagina wet weight and glycogen content; pituitary weight; histology	No effects after gavage of 1.5 mg/kg bw/day for 30 days although transient clinical signs were present.

The weight of evidence from these studies as well as negative results from guideline acceptable reproductive and developmental toxicity tests show that endosulfan is negative for endocrine activity in mammals. EFED’s statement that endosulfan’s *“ability to bind to the receptor at all renders the chemical capable of competing with the endogenous hormone and capable of eliciting hormone-like effects*,” is incorrect and should be deleted.

Page 170

EPA comment: *Exogenous agents that interfere with the production, release, transport, metabolism, binding, action or elimination of endogenous hormones responsible for homeostasis and the regulation of developmental processes in organisms have been referred to as endocrine disruptors (Ankley et al. 1998). Any exogenous agent that causes adverse effects in an intact organism or its progeny, consequent to changes in endocrine function, qualifies as an endocrine disruptor (Gillesby and Zacharewski 1998). Based on this definition and the ability of endosulfan to bind to the estrogen receptor, endosulfan is classified as an endocrine disruptor.*

ETF Response: The ETF respectfully request that this statement be deleted. The above referenced definitions of an endocrine disrupter are similar to those proposed and agreed upon by

EDSTAC and EDTA. Both definitions specifically state that an endocrine disrupter causes adverse effects in an **intact organism** via the endocrine system. Reports from both EDSTAC and OECD's EDTA Task Force have discussed at length the importance of evaluating chemicals in intact organisms before a final determination can be made regarding its potential as an endocrine disrupter. Therefore, EFED's conclusion that endosulfan be classified as an endocrine disrupter based solely on results from a few *in vitro* assays, without regard for the balance of evidence from extensive *in vivo* screens and tests, is scientifically inappropriate and incorrect. In addition, the HED Chapters for endosulfan stated that *"the EPA has not yet developed the criteria it will use for characterizing endocrine disrupting substances, and conclusion by EPA as to whether endosulfan is an endocrine disrupter can not be made at this time. When EPA develops its criteria for characterizing endocrine disrupting chemicals and proceeds with implementing its Endocrine Disrupter Screening Program, these studies will be reviewed, and a determination will be made as to whether endosulfan is an endocrine disrupter and if further testing is needed*".

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EPA Comment: *Whether the toxicity endpoints observed during chronic toxicity studies of endosulfan are a result of endocrine disruption in non-target organisms is not known. However, it is clear that organisms treated with endosulfan did exhibit some toxic effects that have historically been associated with endocrine disrupting chemicals, e.g., developmental effects (Ankley et al. 1998).*

ETF Response: There is no indication from guideline acceptable developmental toxicity studies that endosulfan exposure resulted in any developmental effects. HED has thoroughly evaluated data on the developmental and reproductive toxicity of endosulfan in mammals. HED determined that endosulfan was not a developmental or reproductive toxicant, and concluded: "*The data base is complete and there are no data gaps pertaining to developmental or reproductive toxicity. The data provided no indication of increased sensitivity of rats or rabbits to in utero and post-natal exposure to endosulfan.*" In addition, based on criteria established by the OECD to evaluate endocrine-related effects in developmental and reproductive toxicity tests, endosulfan was negative for endocrine activity in all guideline studies for both adults (Table 2) and offspring (Table 3).

Table 2: Endosulfan - Endocrine endpoints in required toxicity studies in vivo: Adults

Endpoints	Subchronic .				Developmental		2.Gen. Repro.	Chronic/ Carcinogenicity	
OECD-Guideline Number	408		410	452	414		416	453	
Species	Rat	Mouse	Rat	Dog	Rat	Rabbit	Rat	Rat	Mouse
Reproduction							Neg.		
Fertility							Neg.		
Fecundity							Neg.		
Gestation length					neg.	neg.	Neg.		
Abortion					neg.	neg.	Neg.		
Premature Delivery					neg.	neg.	Neg.		
Difficult labor							Neg.		
Time to mating.				.			Neg.		
Mating and sexual behavior							Neg.		
Estrus cycle							Neg.		
Ovulation	neg.	neg.	neg.	neg.			Neg.	neg.	neg.
Spermatogenesis	neg.	neg.	neg.	neg.			Neg.	neg.	Neg.
Sperm count									
Gonad development	neg.	neg.	neg.	neg.	neg.	Neg.	Neg.	neg.	Neg.
Secondary sexual characteristics (muscle mass)	neg.	neg.	neg.	neg.			Neg.	neg.	Neg.
Gross pathol. Of repro. Organs	neg.	neg.	neg.	neg.	neg.	neg.	Neg.	neg.	Neg.
Histology reproductive organs	neg.	neg.	neg.	neg.			Neg.	neg.	Neg.
Hormone levels									
Major sex differences	neg.	neg.	neg.	neg.			Neg.	neg.	neg.
Endocrine tumor incidence	neg.	neg.	neg.	neg.			Neg.	neg.	neg.

Table 3. Endosulfan - Endocrine endpoints in required toxicity studies *in vivo:* Offspring

Endpoints	Developmental Toxicity		2-Generation Reproduction
OECD-Guideline Number	414		416
Species	Rat	Rabbit	Rat
Sexual differentiation	Neg.	Neg.	neg.
Offspring sex ratio	Neg.	Neg.	neg.
Gonad development (size, morphology, weight)	Neg.	Neg.	neg.
Accessory sex organ development	Neg.	Neg.	neg.
Accessory sex organ function (secretory chems.)	-	-	neg.
Sexual development/maturation (vaginal opening, testes descent (cryptorchidism), preputial separation, nipple development)	-	-	neg.
Malformations genital tract	neg.	neg.	neg.
Gross pathology of reproductive tissues	neg.	neg.	neg.
Histology reproductive tissues .	-	-	neg.
Viability of the conceptus	-	-	neg.
Viability of the offspring (neonatally)			neg.
Growth of the conceptus (weight)	neg.	neg.	neg.
Growth of offspring	neg.	neg.	neg.
Major sex differences	-	-	neg.
	neg.	neg.	neg.

The *in vivo* toxicity studies unequivocally show that endosulfan does not cause endocrine activity:

a) Subchronic studies on rats, mice and dogs: No effects were found on endocrine or reproductive organs. Hormone levels were not measured in these studies. However, the

major consequences of hormonal changes were determined: organ weight changes of the endocrine organs such as pituitary, uterus, ovaries, adrenals, mammary gland, testes, thyroid, epididymides, seminal vesicles, vagina (MRID# 00145668, 00147182, and 41099501).

b) Chronic studies on rats and mice: In lifetime exposure studies, minor hormone related effects of a test substance would become evident. However, in guideline acceptable studies endosulfan did not cause any changes or increased tumor incidence in endocrine or related organs (MRID# 41099502 and 40792401)

c) Developmental toxicity studies on rats and rabbits: Treatment during organogenesis did not affect the development and maturation of any endocrine system **(**MRID# 43129101 and 00094837).

d) Two generation reproduction study on rats: This study measures possible disturbances of reproductive performance, development and maturation including development of sex organs (vaginal opening, testis descent, cryptorchidism, etc.) at doses up to and including parental toxicity. Endosulfan, administered to both male and female rats, did not cause such interference through two successive generations (MRID# 00148264**).** There was an indication of weight effects on the pituitary gland of the F_0 pups of the first mating and uterus of the F_{1b} pups from the first mating. These effects are of limited significance since neither the pituitary or uterus was seen as a target organ in any other study, there was no supporting histopathological changes noted, nor were these effects consistent across generations. In addition, four separate uterotrophic assays were negative for uterine effects at doses up to 100 mg/kg bw/day, suggesting that the weight-of-evidence is negative for specific endocrine effects on the uterus. Lastly, the statistically significant increase in pituitary weights was due to a single female in the high dose group. Therefore, the results indicate that endosulfan does not cause disruption of the endocrine system in parents or offspring at dietary dose levels up to and including 75 ppm (3 - 6 mg/kg bw/day), a toxic level in adult animals.

Based on the results summarized above, the evidence clearly shows that endosulfan is negative for all endocrine-related effects. EFED's statement that "organisms treated with endosulfan did exhibit some toxic effects that have historically been associated with endocrine disrupting chemicals, *e.*g., developmental effects," is not supported by the majority of data and should be deleted.

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EPA Comment: *Whether the toxicity endpoints observed during chronic toxicity studies of endosulfan are a result of endocrine disruption in nontarget organisms is not known.*

ETF Response: Only in-vitro studies indicate a low affinity of endosulfan to the endocrine receptors. In-vivo studies including a vitellogenin study in fish indicate that there is no endocrine disruption by endosulfan (Heusel, 1999; MRID# 45218801).

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EPA Comment: *Exposure to endosulfan has resulted in both reproductive and developmental effects in non-target animals. Tadpoles exposed to endosulfan for 96 hours followed by a 10-day recovery period exhibited significantly higher post-exposure mortality (Berrill et al. 1998). Mean length of unexposed tadpoles was significantly larger ($P < 0.01$) than the mean length of tadpoles exposed to 0.132 mg/L endosulfan. Relative to controls,*

endosulfan-treated tadpoles had impaired development and failed to metamorphose. The study concluded that at concentrations likely to be encountered in the environment, 2-week-old tadpoles exhibited greater sensitivity of post-hatching development of the neuromuscular system.

ETF Response: The tadpole experiments (BERILL, 1998) cited do not necessarily prove endocrine disruption (the authors of the studies did not make such a conclusion either). Reported hyperactivity and paralysis indicates toxic effects. Such toxic effects in early developmental stages could be the reason for length differences. Not all developmental effects are necessarily caused by endocrine disruption. Therefore the study citation should be deleted as proof for endocrine disruption.

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EPA Comment: *Additionally, studies on the inter-sexuality of the genital system in birds revealed that endosulfan impaired the development of the avian genital tract (Lutz and Lutz-Ostertag 1975).*

ETF Response: Reference to the work of Lutz and Lutz-Ostertag should be deleted. The researchers exposed the embryos of chicken and quail by either immersing or injecting eggs. This route of exposure is far from a real world situation. Additionally, as endosulfan is cytotoxic, it cannot be concluded with certainty if the observed effects were caused by endocrine disruption or by cytotoxicity.

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EPA Comment: *In mammalian studies, endosulfan increased the rate of testosterone biotransformation and clearance (Wilson and LeBlanc 1997) and has exhibited proliferative, estrogen-like effects in MCF7 cells at doses of 4 ppm (Soto et al., 1994). Endosulfan produced testicular atrophy in male rats fed a diet containing 10 ppm (NCI 1978; Gupta and Gupta 1979) and lowered gonadotropin and testosterone plasma levels. Recent studies (Dalsenter et al. 1999) have also demonstrated that daily sperm production was permanently decreased in rat offspring treated with 3 ppm endosulfan in utero and during lactation.*

ETF Response: There are several non-guideline studies in the public literature which claim isolated findings such as testicular atrophy, characterized by degeneration and necrosis of seminiferous tubules; increased steroid metabolism; and reduced sperm count. The significance of these findings is unclear since in most cases details on methods and characterization of test substance are often not adequately defined, and these results are not supported by guideline accepted studies. One factor that must be considered is whether effects noted in these studies were due to severe intoxication resulting from administration of doses in excess of the maximum tolerated dose (MTD). This was definitely the case in the 1978 National Cancer Institute (NCI) chronic study in rats where both the low and high dose exceeded the MTD, with 38% and 50 % mortality, respectively.

In cases where the doses were high enough to produce serious intoxication, the observed endocrine effects were likely secondary to adverse effects at a non-endocrine target tissue. One example of this involves toxicity to the liver, which then has a distal effect on the endocrine system. The effects of endosulfan on the liver are well documented,

where exposure to high dose levels markedly induces microsomal enzyme activity. Induction of enzyme activity can increase metabolic clearance of endogenous hormones, resulting in lower blood levels and subsequently a compensatory increase in pituitary hormone secretion to maintain homeostasis within an endocrine axis. Enzyme inducers are also known to have effects on the hepatic metabolism and clearance of steroids such as corticosterone. They can also affect androgen-metabolizing enzymes and as such may indirectly affect a number of other major endocrine axes, such as the pituitary - adrenocortical and pituitary - gonadal axes. The mechanism by which a range of liver microsomal enzyme inducers cause thyroid function changes and pathology, including carcinogenesis, is now well understood to be an entirely indirect mechanism that has little relevance to humans.

Therefore, as a result of toxicity elsewhere in the organism, secondary endocrine effects may be functionally and mechanistically linked to alteration in physiological homeostasis and not direct endocrine modulation. The literature studies with positive findings clearly failed to verify the causal-effect relationship to changes in endocrine function.

On the other hand, a large number of proprietary *in vivo* mammalian toxicity studies and published uterotrophic assays indicate that Endosulfan does not elicit modulation of any endocrine organ or system (Tables 1, 2 and 3). Neither morphological nor functional effects on endocrine or reproductive organs, nor any effect on reproductive performance, sexual development, differentiation or maturation, nor activity related to any other endocrinological endpoints was found, even though doses in these studies were applied in the toxic range (Tables 2 & 3).

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EPA Comment: *Endosulfan has demonstrated both reproductive and developmental effects in a broad range of organisms and has been implicated in peer-reviewed literature as an endocrine-disrupting agent. Based on the chronic effects of endosulfan and open literature, EFED recommends that when appropriate screening and/or testing protocols being considered under the Agency's EDSP have been developed, endosulfan be subjected to more definitive testing to better characterize effects related to its endocrine disruptor activity.*

ETF Response: The ETF believes that the data for endosulfan is complete and reliable, including four uterotrophic assays, which is the same assay currently undergoing validation for use as a regulatory screen. The weight-of-evidence from *in vitro* and *in vivo* screening tests and *in vivo* toxicity tests clearly show that endosulfan is not an endocrine disrupter. The ETF believes that until EPA established their own set of criteria for determining endocrine-related effects and has the opportunity to fully evaluate the available data for endosulfan, allegations concerning its potential as an endocrine disrupter should be deleted from the RED.

IV. Information on newly completed, pending and planned studies

In response to requests during the European Community registration process, a number of additional studies with endosulfan were initiated. Some of these studies are available as final reports, others in the evaluation or the reporting phase. In the following is a list of ecological effects studies performed for the European Community.

Test organism	Test substance	Status	Anticipated submission dates
Microcosm	^{14}C Thiodan EC33	Draft in preparation	2nd Quarter '01
Lepomis macrochirus, acute toxicity	^{14}C Thiodan EC33	Finalized	1st Q '01
Lepomis macrochirus, infected with lymphocystis, acute toxicity	^{14}C Thiodan EC33	Draft reports	2nd Q '02
Daphnia magna, acute toxicity	^{14}C Endosulfan-sulfate		2nd Q '02
Oncorhynchus mykiss, acute toxicity	^{14}C Endosulfan-sulfate		2nd Q '02
Cyprinus carpio, acute toxicity	^{14}C Endosulfan-sulfate		2nd Q '02
Daphnia magna, acute toxicity	alpha-endosulfan	Drafts in preparation	2nd Q '02
Daphnia magna, acute toxicity	beta-endosulfan		2nd Q '02
Cyprinus carpio, acute toxicity	alpha-endosulfan		2nd Q '02
Cyprinus carpio, acute toxicity	beta-endosulfan		2nd Q '02
Cyprinus carpio, acute toxicity	Endosulfan-lactone	Drafts in preparation	2nd Q '02
Daphnia magna, acute toxicity	Endosulfan-lactone	Drafts in preparation	2nd Q '02
Cyprinus carpio, acute toxicity	Endosulfan-ether	Drafts in preparation	2nd Q '02
Daphnia magna, acute toxicity	Endosulfan-ether	Drafts in preparation	2nd Q '02
Cyprinus carpio, acute toxicity	Endosulfan-hydroxyether	Drafts in preparation	2nd Q '02
Daphnia magna , acute toxicity	Endosulfan-hydroxyether	Drafts in preparation	2nd Q '02
Long-term aerobic soil metabolism (special design)	Endosulfan sulfate	In progress	1st quarter 2002

V. Appendix 1

Analysis of Available Surface Water Monitoring Data on Endosulfan

A number of national-level and regional-level surface water monitoring data for endosulfan (α- and β-endosulfan) and its major metabolite, endosulfan-sulfate are available from periods as early as 1970. Endosulfan is a well-established insecticide and has been in use for over 30 years, however monitoring data shows no sign of long-term endosulfan accumulation in the environment.

Recognizing its high toxicity to fish, the Endosulfan Task Force (ETF) imposed significant restriction to its use. In addition to restricting its use only to commercial agriculture, the use rates per season was limited to 3 lb a.i./ac and a 300 ft runoff buffer between the treated field and a receiving water body. These restrictions were introduced to endosulfan product labels in July 1987. The California product label contains several statements to avoid and reduce drift to the water bodies. This label was issued to in California users in 1993 and implemented in 1994. Following the label changes the ETF has conducted Product –Stewardship campaigns in California, Arizona and Florida on several occasions between 1994 and 1997. Therefore, instead of simply lumping all the available monitoring data, it should be analyzed in chronological manner. This will highlight the effect of the introduction of the label restrictions on the levels of endosulfan detected in the surface waters.

Surface water monitoring data sources analyzed herein are: EPA-STORET, USGS-NAWQA and California Department of Pesticide Regulations Surface Water Monitoring Data.

EPA-STORET

The EPA-STORET is an extensive database of water quality parameter monitoring conducted across the United States. The source and quality of the data are varied. As pointed out by EFED (Endosulfan Draft RED, Nov. 2000), the database is not reliable enough to conduct detailed quantitative analyses. However, the data can be used for qualitative analysis such as finding the general trend of a water quality parameter on a regional scale. The ETF was not able to acquire the STORET database directly from the EPA, but purchased it from a reseller (EarthInfo, Boulder, CO). The latest version of the STORET available with EarthInfo is 1998 (STORET, 1998) in which data as late as of 1997 was available and is grouped by state.

The database contains several water quality parameters that are related to endosulfan. In this analysis dissolved surface water concentrations of endosulfan (α- and β-endosulfan) and endosulfan sulfate were used. The database was searched for parameter numbers 34351 (Total Endosulfan Sulfate µg/L), 34356 (Total β-endosulfan µg/L), 34361 (Total α- endosulfan, µg/L), 39388 (Total Endosulfan[1] in the Whole water Sample µg/L), and 82354 (Total Endosulfan[1] Dissolved in Water µg/L). Since the source and quality of the data are varied, the reported concentration of parameters are accompanied by qualifying concentration codes (e.g. "A" denotes average of several samples take at the same instance). The concentration codes encountered for the endosulfan data selected from the database are:
(1) blank – indicating a positive quantification of concentration (the LOQ were not available, however),
(2) "K" -- indicating that the actual concentration in the sample is less than the reported concentration, meaning that the levels are below the LOQ for the analysis, and
(3) "U" – indicating that the concentration levels are undetectable under that analysis, ie, below the LOD.

[1] ETF does not have the information if this parameter represents α + β endosulfan or α- + β- + endosulfan sulfate

The standard practice in the case of sample concentrations below LOQ is to multiply the reported concentration by 0.5 and use in the analysis. However, many data points had analysis with LOQ as high as 100 µg/L. This indicates that the sample analysis had poor sensitivity and that data point is not appropriate to be used along with other data with positive quantification. Therefore, data with these three concentration codes were analyzed separately in an attempt to analyze data with comparable Sample Analysis Error together. The data points that had concentration code "U" were not analyzed.

All analyses were carried out for data from California, Florida, Mississippi, Louisiana, Washington, and Ohio as these were the states identified by EFED (Endosulfan draft RED, Nov. 2000) as the states with relatively high detections.

Samples with Positive Quantification

Figures 1-1 to 1-6 show the maximum, minimum and the mean endosulfan concentration quantified each year along with the number of samples with positive quantification for California, Florida, Mississippi, Louisiana, Washington, and Ohio, respectively. It should be noted that α-, β- endosulfan and endosulfan sulfate occurrences were treated independently and were not added on instances that all three were detected and quantified.

The figures show that endosulfan concentrations and number of detections were significantly reduced with time in the six states analyzed. In California, Louisiana, Washington and Ohio endosulfan concentrations after 1990, ranging from 0.009 to 0.095 ppb with a mean of 0.006 ppb across all four states. In Mississippi and Florida there were 174 and 67 positive quantifications, respectively after 1990. However, these concentrations ranged from 0.02 to 0.99 ppb, with a mean of 0.31 ppb across the two states.

Some of the concentrations reported in Mississippi and Louisiana are very suspicious. Concentrations of about 500,000 µg/L were reported before 1990. These samples were all taken by the Army Corps of Engineers. ETF believes that these concentrations would not have resulted from a registered use because a 500,000 µg/L (or 0.5 g/L) concentration corresponds to about 600 kg of endosulfan AI in a one acre hypothetical static water body that is 0.3 m deep. The concentration is also far above the water solubility of 200 µg/L. ETF suspects that this report might have caused due to a data-entry error or analysis error or unit conversion error. It is beyond the scope of the ETF to investigate this beyond this point.

Figure 1-1 Maximum, Minimum and Mean Concentrations of α-, β-Endosulfan and Endosulfan Sulfate and the Number of Samples with Positive Quantification Reported in STORET for California

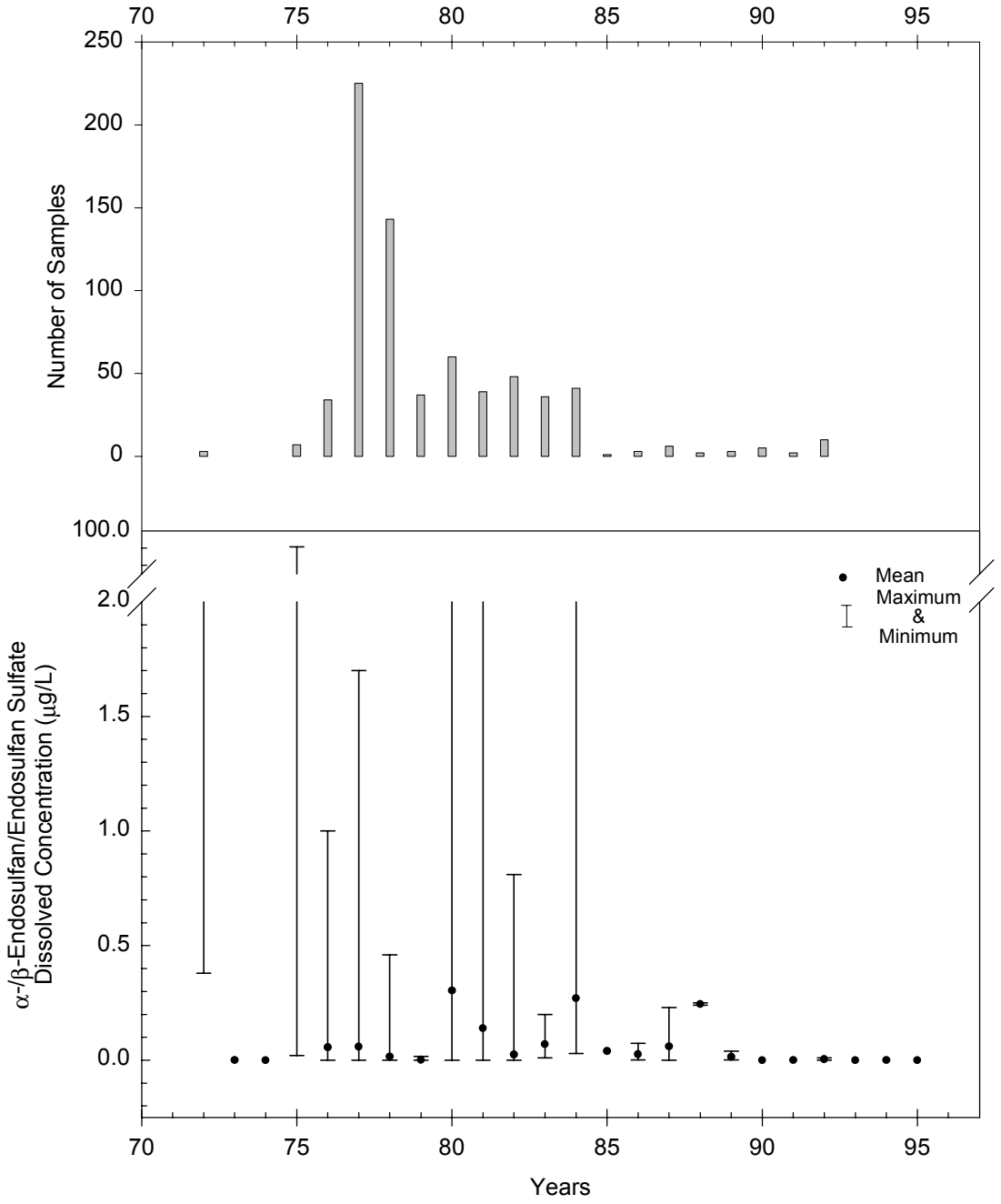


Figure 1-2 Maximum, Minimum and Mean Concentrations of α-, β-Endosulfan and Endosulfan Sulfate and the Number of Samples with Positive Quantification Reported in STORET for Florida

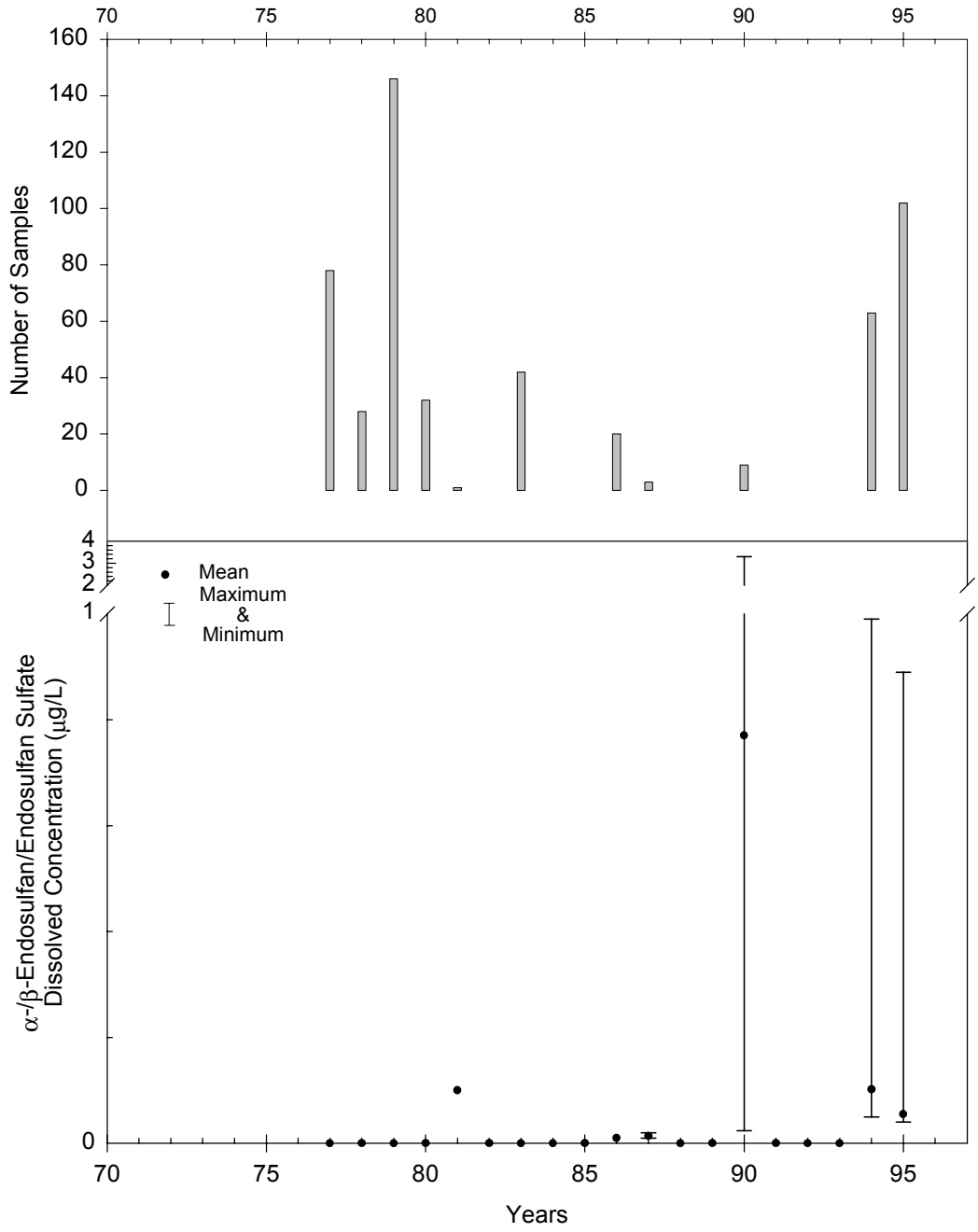


Figure 1-3 Maximum, Minimum and Mean Concentrations of α-, β-Endosulfan and Endosulfan Sulfate and the Number of Samples with Positive Quantification Reported in STORET for Mississippi

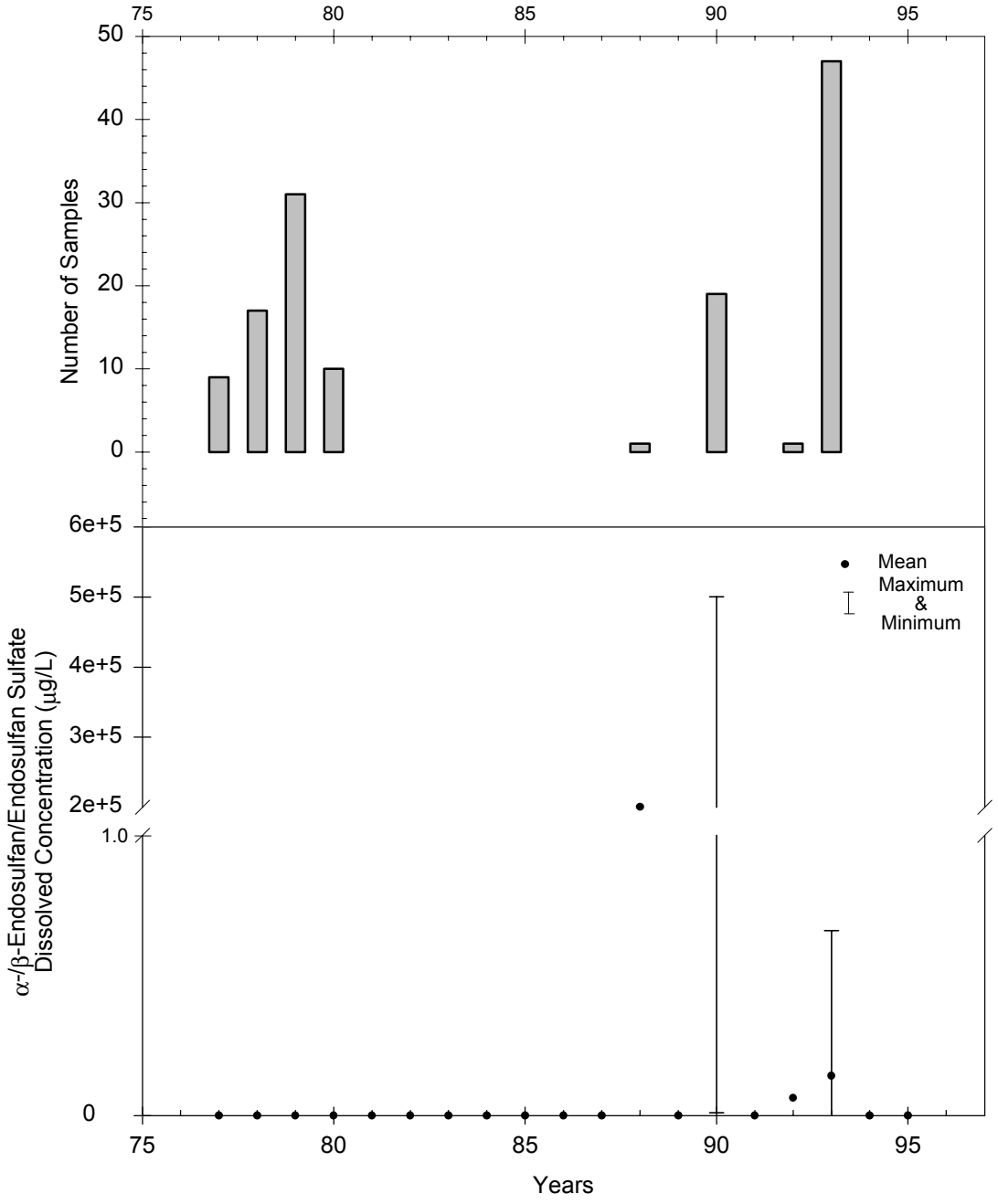


Figure 1-4 Maximum, Minimum and Mean Concentrations of α-, β-Endosulfan and Endosulfan Sulfate and the Number of Samples with Positive Quantification Reported in STORET for Louisiana

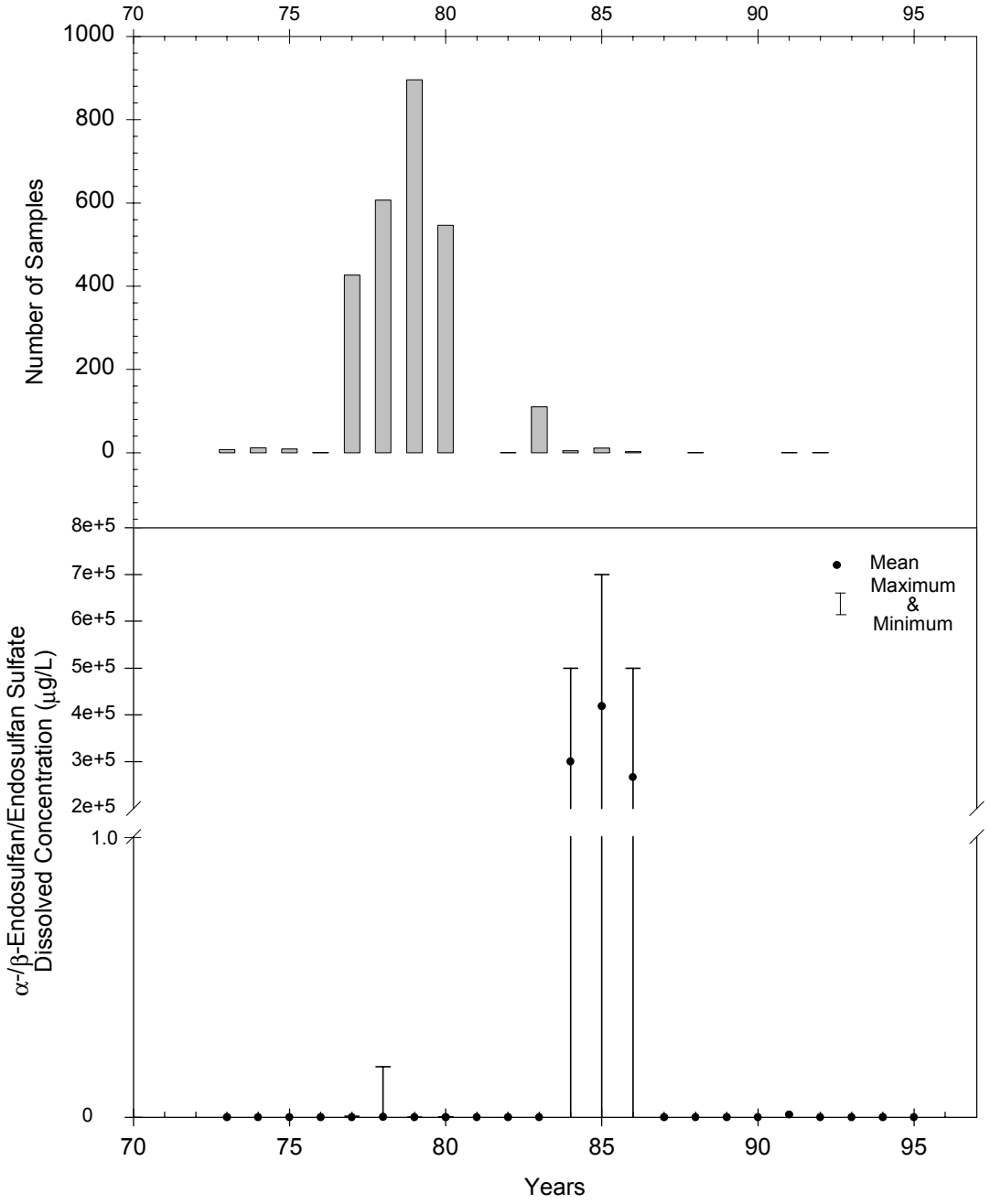


Figure 1-5 Maximum, Minimum and Mean Concentrations of α-, β-Endosulfan and Endosulfan Sulfate and the Number of Samples with Positive Quantification Reported in STORET for Washington

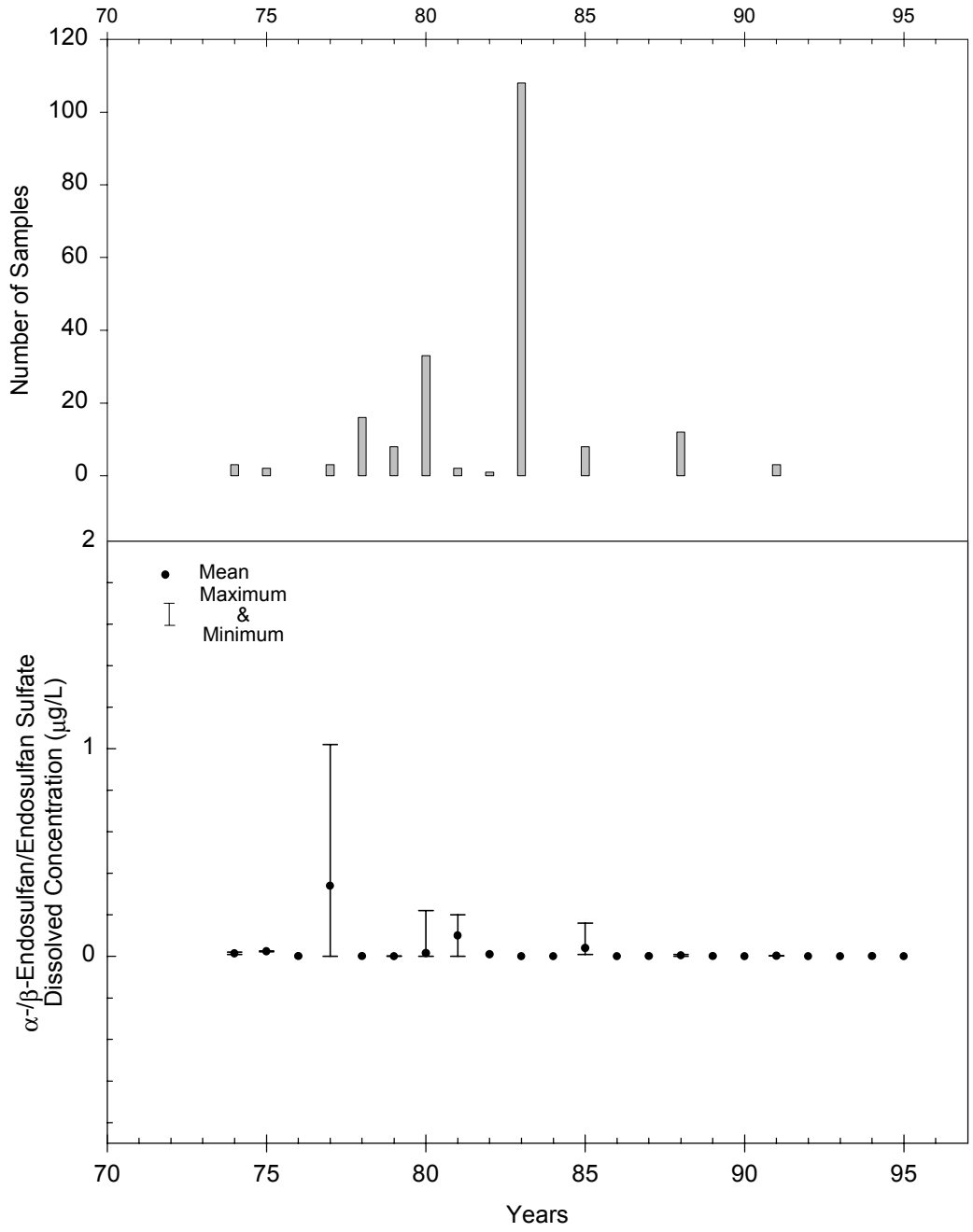
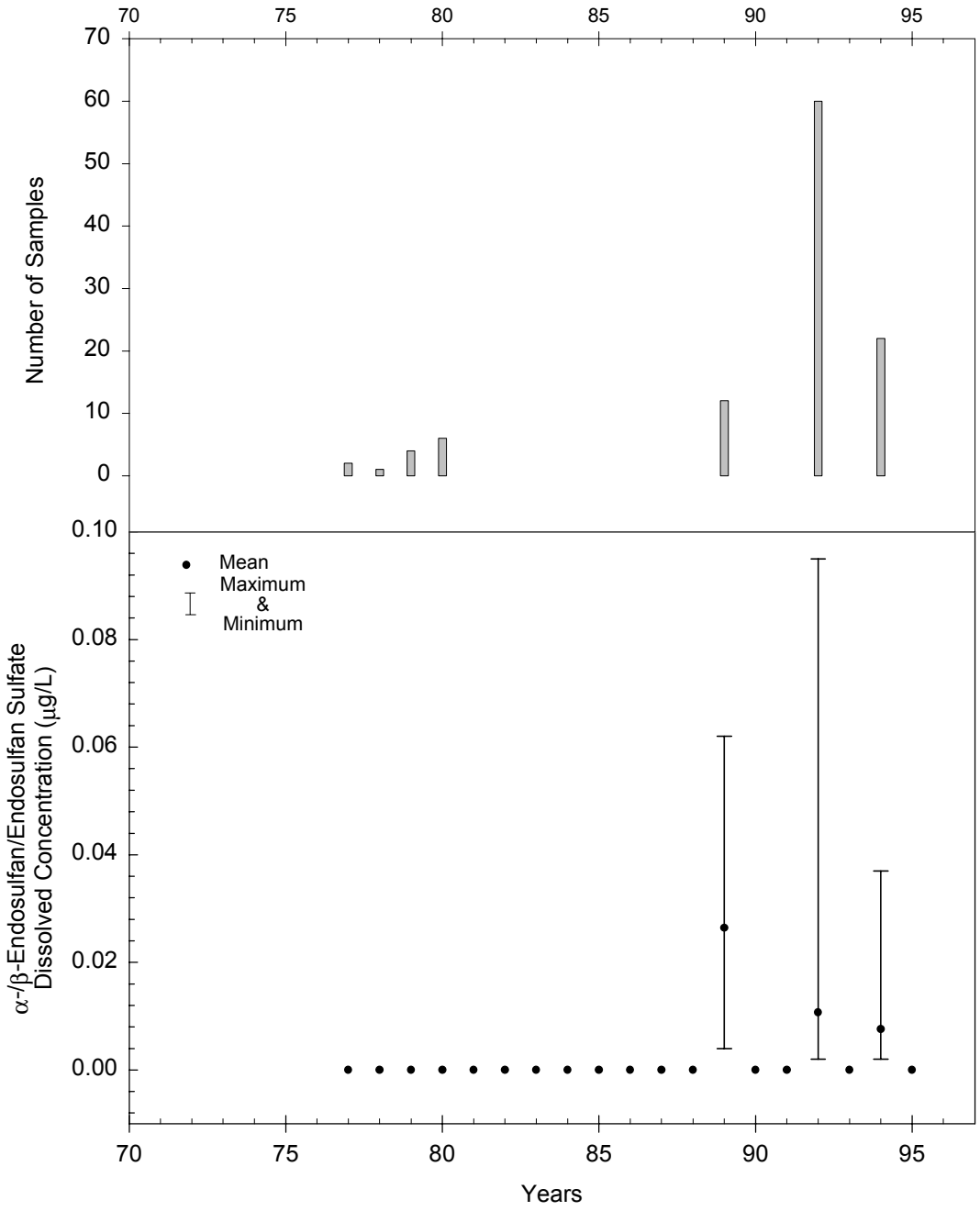


Figure 1-6 Maximum, Minimum and Mean Concentrations of α-, β-Endosulfan and Endosulfan Sulfate and the Number of Samples with Positive Quantification Reported in STORET for Ohio



Samples with Positive Detection but below level of quantification

The data points that showed positive detection were divided into four categories – (1) LOQ less than 0.01 µg/L, (2) LOQ 0.01 to 1.0 µg/L, (3) LOQ 1.0 to 10.0 µg/L, and (4) LOQ greater than 10 µg/L. Figures 1-7 to 1-12 show the number of sample points under each of the above four categories in California, Florida, Mississippi, Louisiana, Washington, and Ohio, respectively.

The figures consistently show that the number of endosulfan detection significantly reduced in all the six states after the introduction of use restrictions (1989 to 1990).

Figure 1-7 Analysis of Data Points with Positive Endosulfan and Endosulfan Sulfate Detection in California

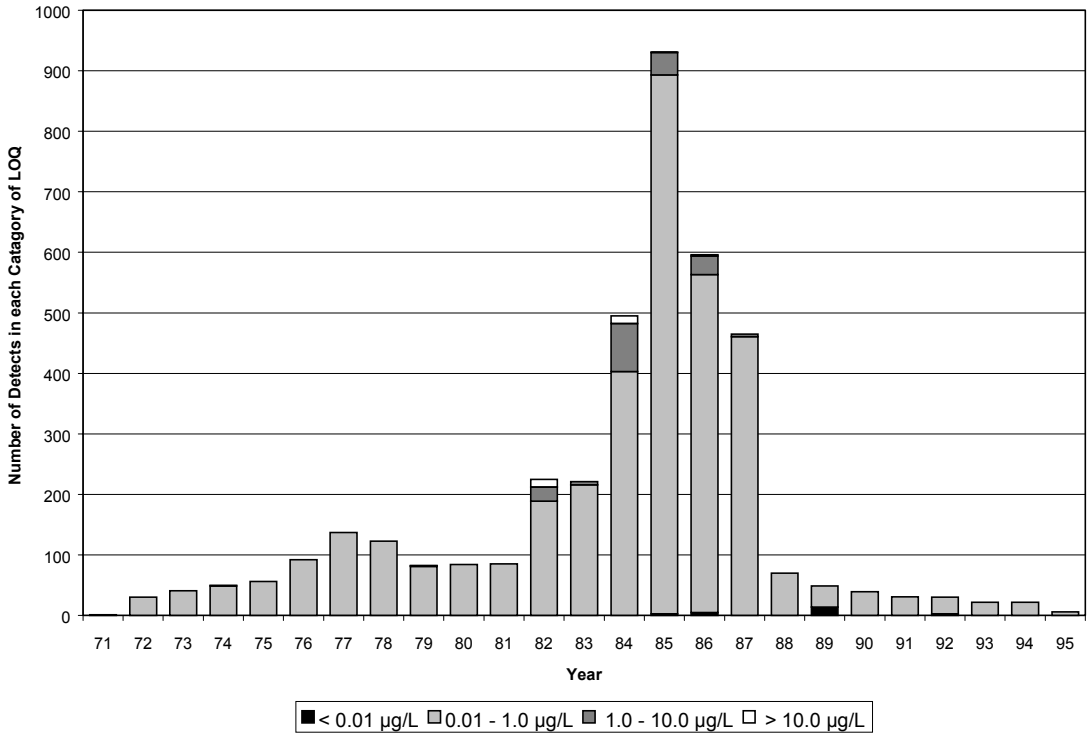


Figure 1-8 Analysis of STORET Data Points with Positive Endosulfan and Endosulfan Sulfate Detection in Florida

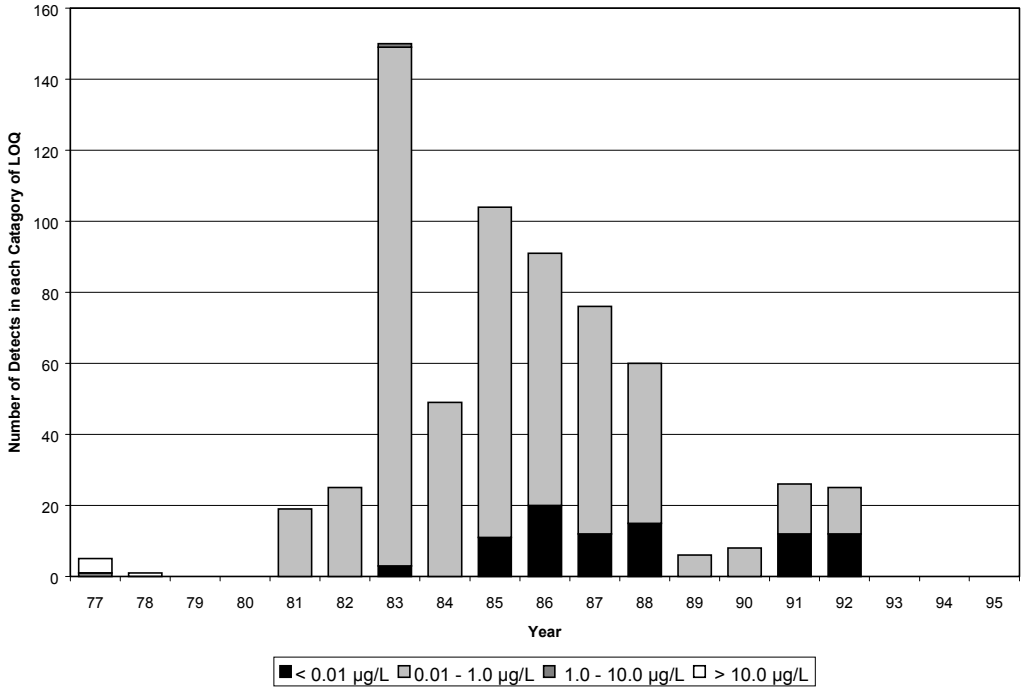


Figure 1-9 Analysis of STORET Data Points with Positive Endosulfan and Endosulfan Sulfate Detection in Mississippi

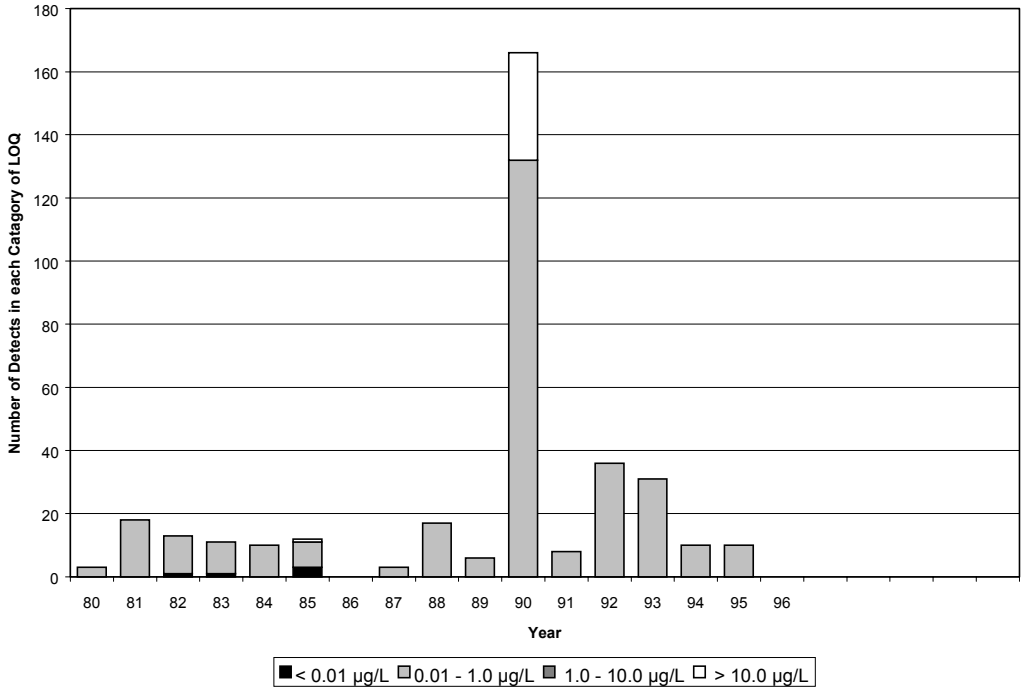


Figure 1-10 Analysis of STORET Data Points with Positive Endosulfan and Endosulfan Sulfate Detection in Louisiana

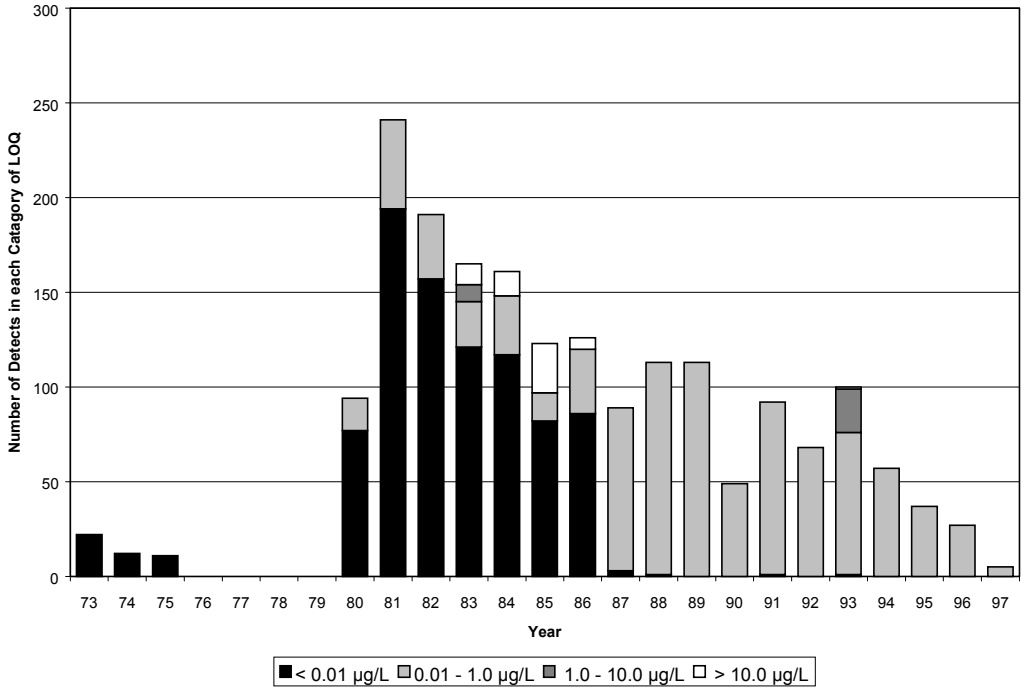


Figure 1-11 Analysis of STORET Data Points with Positive Endosulfan and Endosulfan Sulfate Detection in Washington

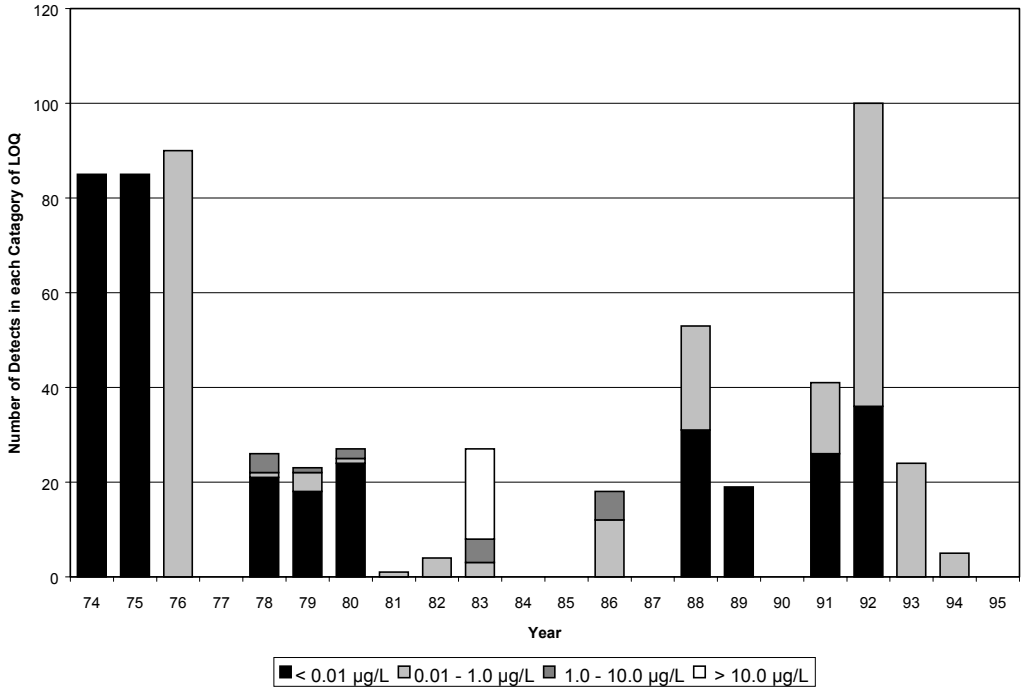
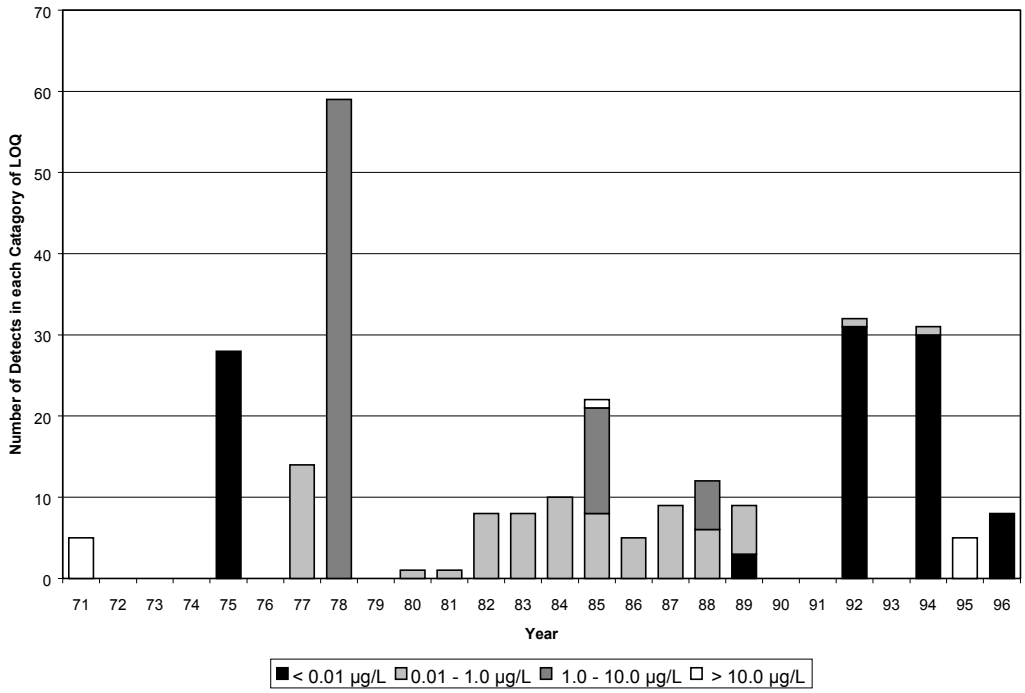


Figure 1-12 Analysis of STORET Data Points with Positive Endosulfan and Endosulfan Sulfate Detection in Ohio



USGS-NAWQA

The USGS started its National Water Quality Assessment (NAWQA) program in 1991 in order to collect chemical, biological, and physical water quality data from study Units (river basins) across the US (Williamson et al., 2000). Figure 1-13 shows the NAWQA study units and their initiation periods. In 1999 USGS developed an online data warehouse to distribute the NAWQA data and is available at http://water.usgs.gov/nawqa/data. Surface water quality data for endosulfan (Parameter 39388 – Total dissolved Endosulfan in µg/L) was extracted from this data source. The highest concentration detected from 1991 to 1997 was 0.006 µg/L. About 90 % of the data points showed Total Endosulfan concentration below the LOQ of 0.001 µg/L.

California DPR Surface Water Database

The California Department of Pesticide Regulations published its surface water database and is now available at http://www.cdpr.ca.gov/docs/surfwatr/surfdata.htm and also in CD-ROM. This database contains water quality data from 16 counties in California sampled from January 1991 through March 2000. Endosulfan and endosulfan sulfate data was derived from this database and analyzed. Figure 1-14 shows that as with STORET data, the California surface water database also shows significantly reduced detection after 1993.

In 1993 a detailed study (Ganapathy et al, 1998) was initiated with a joint effort from California DPR and California Department of Fish and Game (CDFG) monitoring the Sacramento (Nov. 1993 to 1994), Merced (June 1994 to 1995), Salinas (July 1994 to 1995) and the Russian (August 1994 to 1995) Rivers. Water samples were collected from these rivers every week (for one year) and analyzed for insecticide

residues, including endosulfan. It should be noted that endosulfan was not detected in any of the samples collected.

Conclusion

A chronological evaluation of the three databases clearly demonstrates the decline in endosulfan concentrations in surface water with time. The ETF believes that this is clear evidence for the effectiveness of the mitigation measures introduced to the endosulfan labels, (maximum annual use of 3 lb ai/acre + 300 foot buffer between treated area and water courses) together with the ongoing product stewardship in Florida and California. It also demonstrates that endosulfan does not accumulate in surface waters due to the continual abiotic and biological degradation of the compound in aquatic environments, as observed in laboratory studies

Figure 1-13 USGA-NAWQA Study Units Across the US

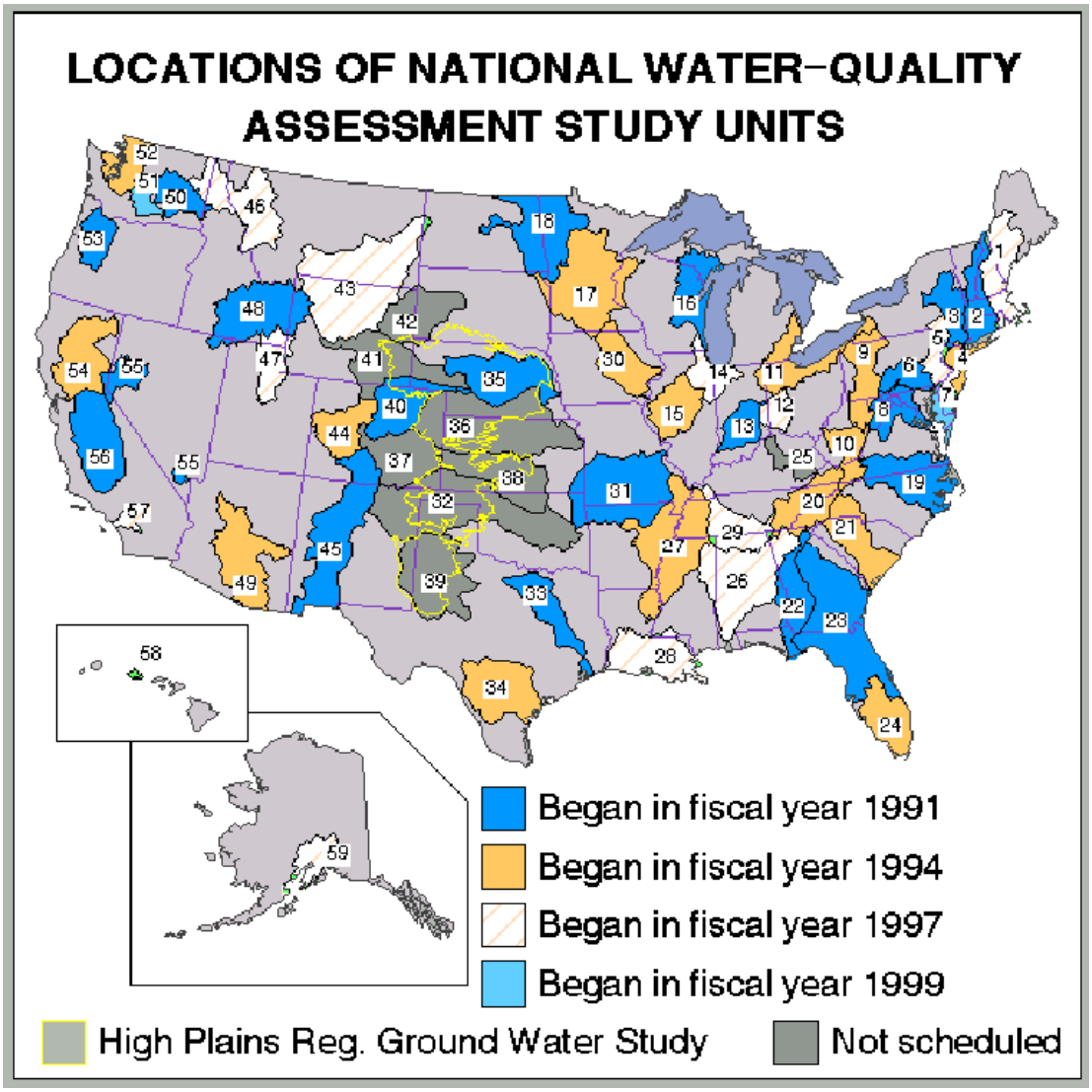
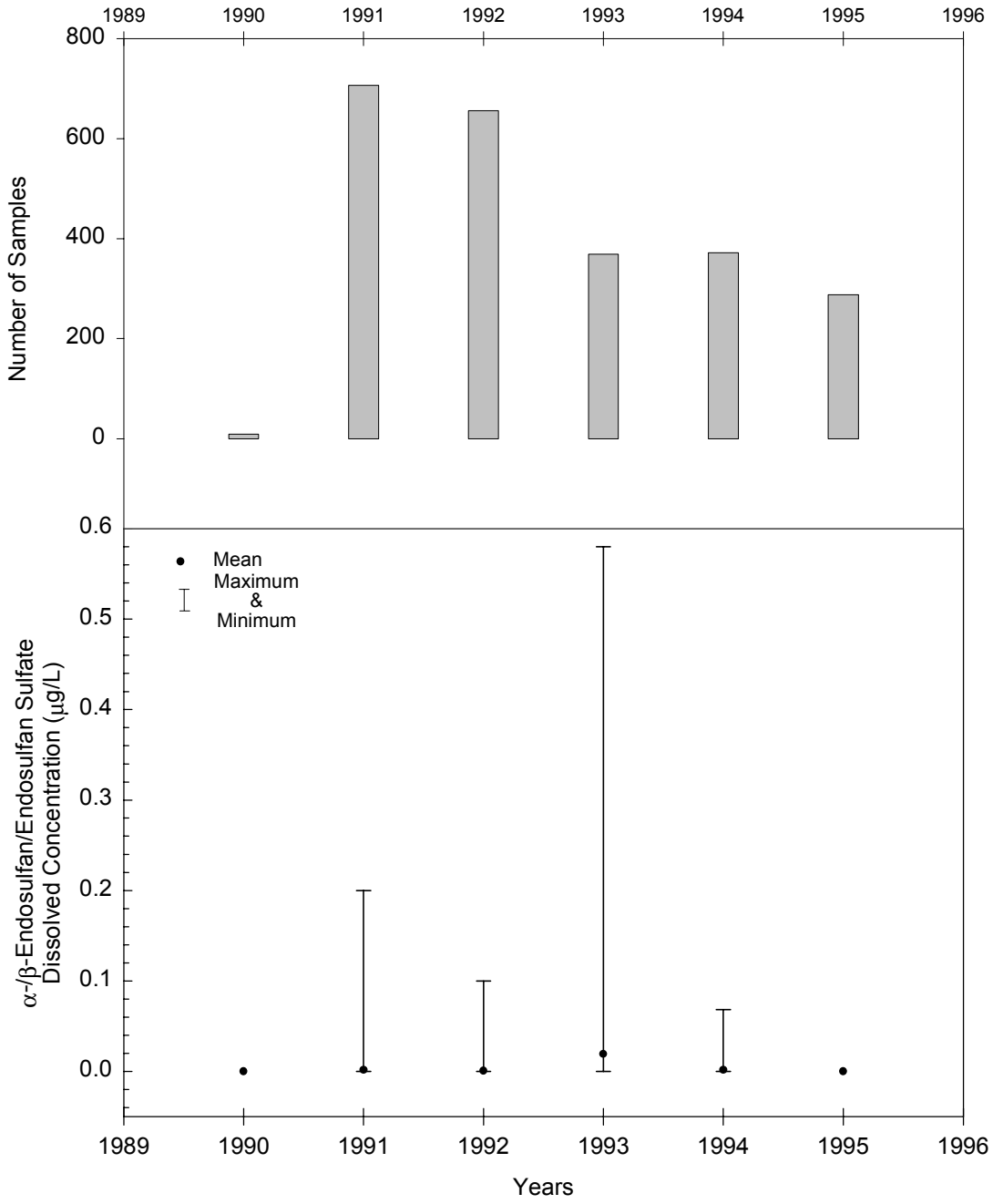


Figure 1-14 Maximum, Minimum and Mean Endosulfan and Endosulfan Sulfate Concentration Quantification Reported in California Surface Water Database



Appendix 1 References

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2. Ganapathy, C., Nordmark, C., Bennet, K. and Bradley, A. 1998. Temporal Distribution of Insecticide residues in Four California Rivers. Report # EH97-06, California Department of Pesticide Regulation, Sacramento, CA.